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Association for Accessible Medicines



AAM White Paper

Nitrosamines

An Industry Position Paper
Based on Risk

OCTOBER 2020

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AAM represents the manufacturers and distributors of finished generic pharmaceutical products; manufacturers and distributors of bulk active pharmaceutical chemicals; and suppliers of other goods and services to the generic pharmaceutical industry. Our members manufacture more than 90% of all generic pharmaceuticals dispensed in the U.S., and their products are used in more than three billion prescriptions every year. Generics represent greater than 90% of all prescriptions dispensed in the U.S., but only 20% of expenditures on prescription drugs. AAM is the sole association representing America's generic pharmaceutical sector.

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Background

Nitrosamines are a group of carcinogens that are formed by the reaction of secondary and tertiary amines, amides, carbamates, and derivatives of urea with nitrite or other nitrogenous agents (including N_2O_3 and N_2O_4)¹. The common nature of the precursors and the facile nature of the nitrosation reactions under acidic and neutral pH² have made nitrosamines a common and an unwelcomed guest in the world of foods, consumer goods, and pharmaceuticals.

The carcinogenic properties of nitrosamines have been known for more than 50 years³ and there are several nitrosamines that have been tested for carcinogenicity and have shown carcinogenic activities N-nitroso-dimethylamine (NDMA), N-nitroso-diethylamine (NDEA), N-nitroso-N-methyl-4-aminobutyric acid (NMBA), N-nitroso-diethanolamine (NDELA), nitroso morpholine (NMOR), N-nitroso-N-methyl-N-ethylamine, and N-nitrosopyrrolidine (NPYR), being some of the well-known among these^{4,5}. Nitrosamines are considered by the ICH M7(R1) guideline as high potency mutagenic carcinogens referred to as compounds that are part of the “cohort of concern” and as such are classified as Class 1 impurities – “known mutagenic carcinogens,” – based on both rodent carcinogenicity and mutagenicity data⁶. They are categorized by the International Agency for Cancer Research (IARC) as 2A and 2B – Probable and Possible Carcinogens⁷, respectively, based on study data of some species.

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- 1 Loepky, R., N.; “Nitrosamine and N-Nitroso Compound Chemistry and Biochemistry: Advances and Perspectives”; *ACS Symposium Series*, 1993, 553, Chapter 1, pp. 1-18. doi:10.1021/bk-1994-0553.ch001.
 - 2 Challis BC, Edwards A, Hunma RR, Kyrtopoulos SA, Outram JR. Rapid formation of N- nitrosamines from nitrogen oxides under neutral and alkaline conditions. *IARC Sci Publ.* 1978;(19):127-142.
 - 3 Preussmann R. Carcinogenic N-nitroso compounds and their environmental significance. *Naturwissenschaften.* 1984;71(1):25-30. doi:10.1007/BF00365976
 - 4 Park JE, Seo JE, Lee JY, Kwon H. Distribution of Seven N-Nitrosamines in Food [published correction appears in *Toxicol Res.* 2018 Oct;34(4):371]. *Toxicol Res.* 2015;31(3):279-288. doi:10.5487/TR.2015.31.3.279
 - 5 Yang C.S., Smith T.J. (1996) Mechanisms of Nitrosamine Bioactivation and Carcinogenesis. In: Snyder R. et al. (eds) *Biological Reactive Intermediates V. Advances in Experimental Medicine and Biology*, vol 387. Springer, Boston, MA. https://doi.org/10.1007/978-1-4757-9480-9_47
 - 6 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; “ICH Harmonised Guideline - Assessment And Control Of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, M7(R1)”; March 31, 2017, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_R1_Addendum_Step_4_2017_0331.pdf
 - 7 International Agency for Research on Cancer; IARC Monographs On The Identification Of Carcinogenic Hazards To Humans”, <https://monographs.iarc.fr/list%20of-classifications/>

hundred nitrosamines have been tested for carcinogenicity. Of all the nitrosamines, NDMA have been researched the most. NDMA have been found to be carcinogenic in more than 20 species of animals and it is believed that no species is exempt from the carcinogenic activity of this compound^{3,8}.

The presence of nitrosamines continues to be problematic in the human environment. Some of the most well-known sources of nitrosamines are tobacco (smoking and chewing)⁹, rubber products¹⁰, cosmetics (creams, lotions, shampoos)¹¹, metal cutting fluids¹², pesticides¹³ and certain pharmaceuticals. Nitrosamines are also present in foods such as bacon, beer, and preserved fish. They can be formed when meats are heated to high temperatures^{4,14,15}. Nitrosamines, including NDMA, NDEA and NPYR, can also be found in drinking water (WHO, 2008, EPA 2016).

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- 8 Concise International Chemical Assessment Document 38; N-Nitrosodimethylamine; First draft prepared by R.G. Liteplo and M.E. Meek, Health Canada, Ottawa, Canada, and W. Windle, Environment Canada, Ottawa, Canada; <https://www.who.int/ipcs/publications/cicad/en/cicad38.pdf?ua=1>
 - 9 Irina Stepanov, Joni Jensen, Dorothy Hatsukami, Stephen S. Hecht, Tobacco-Specific Nitrosamines in New Tobacco Products, *Nicotine & Tobacco Research*, Volume 8, Issue 2, April 2006, Pages 309-313, <https://doi.org/10.1080/14622200500490151>
 - 10 Bryan G. Willoughby, Keith W. Scott; Nitrosamine Formation in Rubber: I. Influence of Mixing History. *Rubber Chemistry and Technology* 1 May 1998; 71 (2); pp. 310–322
 - 11 Duck Soo Lim, Tae Hyun Roh, Min Kook Kim, Yong Chan Kwon, Seul Min Choi, Seung Jun Kwack, Kyu Bong Kim, Sungpil Yoon, Hyung Sik Kim & Byung-Mu Lee (2018) Risk assessment of N-nitrosodiethylamine (NDEA) and N-nitrosodiethanolamine (NDELA) in cosmetics, *Journal of Toxicology and Environmental Health, Part A*, 81:12, pp. 465-480. <https://doi.org/10.1080/15287394.2018.1460782>
 - 12 Loeppky RN, Hansen TJ, Keefer LK. Reducing nitrosamine contamination in cutting fluids. *Food Chem Toxicol.* 1983;21(5):607-613. doi:10.1016/0278-6915(83)90148-5
 - 13 Warren R. Bontoyan, Mark W. Law, and Dallas P. Wright; Nitrosamines in agricultural and home-use pesticides; *Journal of Agricultural and Food Chemistry* **1979** 27 (3), 631- 635. doi:10.1021/jf60223a009
 - 14 Scanlan RA. Formation and occurrence of nitrosamines in food. *Cancer Res.* 1983;43(5 Suppl):2435s-2440s.
 - 15 Hotchkiss JH. Preformed N-nitroso compounds in foods and beverages. *Cancer Surv.* 1989;8(2):295-321

Nitrosamines are also formed endogenously, in our body, including the stomach and oral cavity^{16,17}, which provides an environment suitable for nitrosation based on our intake of amines and nitrites as well as nitrates.

Nitrosamines are present in pharmaceuticals. Two well-known, efficacious anti-tumor drugs, carmustine and lomustine, have nitrosamines in their chemical structures. are also known to form endogenously based on the structure of certain drugs. Nitrates that we consume produce nitrites and other oxides of nitrogen *in vivo*, mediated by reductase enzymes and nitric oxide synthase (NOS)^{18,19} may cause nitrosation of amines. In addition, simultaneously feeding animals secondary amines and nitrites has led to formation of tumors. Elimination of NDMA and N-nitrosoproline (NPRO) in human urine is evidence of endogenous nitrosation²⁰. There are numerous approved drug products (DP) like amitriptyline, clomiphene, clomipramine, dextropropoxyphene, diphenhydramine, disopyramide, erythromycin, mepyramine, methapyrilene, penicillin G procaine salt, procaine, tamoxifen, trimeprazine, tripeleminamine, minocycline, and aminopyrine that are known to undergo endogenous nitrosation and generate volatile nitrosamines like NDMA *in vivo*.^{21,22}

16 Bartsch H, Pignatelli B, et. al., Inhibitors of endogenous nitrosation mechanisms and implications in human cancer prevention, *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 1988, 202(2), pp. 307-324

17 Mirvish SS. Formation of N-nitroso compounds: chemistry, kinetics, and in vivo occurrence. *Toxicol Appl Pharmacol*. 1975;31(3); pp.325-351.

18 Brambilla G, Martelli A. Update on genotoxicity and carcinogenicity testing of 472 marketed pharmaceuticals. *Mutat Res*. 2009;681(2-3); pp.209-229

19 Heinrich TA, da Silva RS, Miranda KM, Switzer CH, Wink DA, Fukuto JM. Biological nitric oxide signalling: chemistry and terminology. *Br J Pharmacol*. 2013;169(7):1417-1429. doi:10.1111/bph.12217

20 Leaf CD, Wishnok JS, Tannenbaum SR. Mechanisms of endogenous nitrosation. *Cancer Surv*. 1989;8(2):323-334.

21 Mirvish SS. Formation of N-nitroso compounds: chemistry, kinetics, and in vivo occurrence. *Toxicol Appl Pharmacol*. 1975;31(3):325-351. doi:10.1016/0041-008x(75)90255-0.

22 Brambilla G, Martelli A. Update on genotoxicity and carcinogenicity testing of 472 marketed pharmaceuticals. *Mutat Res*. 2009;681(2-3):209-229. doi:10.1016/j.mrrev.2008.09.002

Impact of Recent Developments Related to Nitrosamines on the Pharmaceutical Industry

Nitrosamines have once again become a focus of global regulatory agencies, including FDA, due to the discovery of trace amounts of these compounds in a class of drugs known as angiotensin II receptor blockers (ARB), frequently referred to as “sartans.” The “sartan” molecules involved include valsartan, losartan, irbesartan, azilsartan, olmesartan, eprosartan, candesartan, and telmisartan. Valsartan and losartan were the most severely affected due to their market share when several lots were recalled²³. Subsequently there were recalls of other histamine H₂-receptor antagonists like ranitidine and nizatidine, which were found to contain NDMA as both a process impurity and degradant²⁴. In addition, FDA, European Medicines Agency (EMA), and other global authorities have confirmed the presence of NDMA in metformin and pioglitazone, which are used widely for Type II diabetes²⁵. In February 2020, FDA posted results of analysis of metformin products, which showed no detectable to low levels of NDMA in the lots tested. However, in May 2020, FDA recommended that several lots of metformin extended-release tablets be withdrawn from the market due to the presence of trace amounts of NDMA²⁶.

FDA has been working diligently to address the concerns created by the presence of nitrosamines in DPs and keeping the public informed. Recent actions have included the recall of certain lots of DPs, publication of acceptable daily exposure limits of

23 U.S. Food and Drug Administration; “FDA updates on angiotensin II receptor blocker (ARB) recalls including valsartan, losartan and irbesartan”; <https://www.fda.gov/drugs/drugsafety/ucm613916.htm>;

24 FDA Updates and Press Announcements on NDMA in Zantac (ranitidine), <https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine>

25 Update on nitrosamine impurities: EMA continues to work to prevent impurities in medicines, 26th April, 2019, https://www.ema.europa.eu/en/documents/press-release/update-nitrosamine-impurities-ema-continues-work-prevent-impurities-medicines_en.pdf

26 FDA Updates and Press Announcements on NDMA in Metformin, <https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin>

nitrosamines in the DPs in question and the development, and publication of sensitive analytical methods for the determination of nitrosamines^{27,28}. FDA has defined the acceptable daily exposure limit for NDMA to be 96 ng/day and for NDEA to be 26.5 ng/day²³. For NMBA, which was identified more recently, the safety level has been also determined at 96 ng/day. The assessment, testing, and remediation related to nitrosamine impurities in the sartans, ranitidine, and other drugs has required significant additional resource allocation from the pharmaceutical industry, as well as from FDA.

This situation has created uncertainty for FDA, industry, and consumers. It has shaken consumers' confidence in the safety of the medications they have come to trust and depend on to maintain the quality of their lives. The impact on the generic pharmaceutical industry has been especially disconcerting, as most of the affected drugs are genericized. Generics represent, by volume, 90% of all prescriptions dispensed in the U.S. There are more than 15,000 approved generic prescription products listed in the active section of the FDA Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Cumulative Supplement, Version November 2019²⁹.

Many of the global regulatory authorities, including WHO³⁰, EMA³¹ and Health Canada³² have provided directives regarding evaluation of nitrosamines in products including complete retrospective analysis of all approved DPs. In the opinion of the industry, this kind of blanket analysis would be a Herculean task in

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- 27 LC-HRMS Method for the Determination of Six Nitrosamine Impurities in Losartan Drug Substance or Drug Product, <https://www.fda.gov/media/125478/download>
 - 28 GC/MS Headspace Method for Detection of NDMA in Valsartan Drug Substance and Drug Products, <https://www.fda.gov/media/115965/download>
 - 29 Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, <https://www.accessdata.fda.gov/scripts/cder/ob/>
 - 30 Information Note Nitrosamine impurities, World Health Organization; https://www.who.int/medicines/publications/drugalerts/InformationNote_Nitrosamine-impurities/en/
 - 31 Questions and answers on "Information on nitrosamines for marketing authorisation holders, EMA/CHMP/428592/2019 Rev. 3; 27th March 2020. https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-information-nitrosamines-marketing-authorisation_en.pdf
 - 32 Health Canada expands efforts on nitrosamine impurities. *Reactions Weekly*, 1783, 4 (2019). <https://doi.org/10.1007/s40278-019-72487-3>

view of the fact that every approved DP will need to be evaluated for the kinds of nitrosamines that it could potentially harbor based on the structure of the active pharmaceutical ingredient (API), nature of excipients, manufacturing of API and the DP; safety levels of these nitrosamines will need to be ascertained based on the maximum daily dose of the DP and sensitive analytical methods established for their analysis. This approach has the potential of diverting a significant amount of the resources and focus of the generics industry from continuing to bring timely affordable and efficacious drugs to the American public. Moreover, the diversion of the limited resources with the added regulatory burden may stifle future research and development capabilities of more complex generic products that could lead to concerns related to sustainability for the generics industry in the long term³³. Further, the industry is concerned the additional burden could potentially negatively affect FDA's ability to meet its user fee commitments, to review and approve generic drug applications to ensure timely access to more affordable generic medicines. The generics industry is also concerned with the potential of escalating situations of drug shortage if a non-risk-based approach is adopted.

With the above issue in mind, the generics industry is proactively proposing a science-driven alternative to complete retrospective analysis of all DPs approved to date for possible presence of nitrosamines. The proposal is a risk-based approach for the evaluation of nitrosamines in drugs, by actively looking into the source of nitrosamines in DPs to mitigate risk. This approach would ensure products that are at risk of nitrosamine are tested to achieve the safety standards set forth by FDA and other global regulators. With a risk-based approach, the sponsors will perform an evaluation of the potential source(s) of nitrosamine(s) based on the API structure, manufacturing of the APIs, DPs, excipients, packaging and other factors to determine the level of risk (risk profile) associated with the DP. Based on the risk profile, the sponsors will determine the controls to reduce the related risk(s). The industry will aspire to look beyond the intrinsic nature of the APIs and into the nature and quality of the reagents and solvents, even those excipients used relatively upstream in the manufacturing process, for assuring the quality of the API as well as the DP.

33 AAM White Paper – Ensuring the Future of Accessible Medicines in the US. https://accessiblemeds.org/sites/default/files/2018-02/AAM-Whitepaper-Ensuring-Future-of-Generic-Medicines.pdf?_ga=2.36274345.846023477.1600113565-1698144257.1555957095

Proactive Actions Proposed by the Generic Pharmaceutical Industry to Mitigate Nitrosamine Related Challenges to Assure Patient Safety

The generics industry proposes a streamlined approach to reduce the presence of nitrosamines in their DPs based on better understanding of the source of these impurities. The risk evaluation will take into account all aspects of the development of the DP throughout its life cycle.

- Adopting this approach, the generics industry proposes a universal guideline based on the scientific understanding of the source and risk related to nitrosamines to assess and manage the levels of nitrosamines in the DP. The assessment will take into account the scientific understanding of the process. For instance, the determination of whether the source of the nitrosamine lies in the structure of the API itself or the excipients or general external sources like the reagents and solvents, including water, used in the manufacturing process; parts of the packaging that could be made from rubber or elastomers, nitrocellulose and other components that can give rise to nitrosamines. For example, if the cleaning process for the manufacturing equipment is known to give rise to nitrosamines, a control will be set for that process. Similarly, if the water used in the manufacturing process is for cleaning and is determined to be the source of some nitrosamines, appropriate controls will be set. In other words, the process by which the nitrosamines are controlled will be based on the understanding of whether they are process impurities in the API, including possible degradants in the API and DP, which could increase over shelf life, or arising due to external factors like cleaning, which can be independently controlled.
- Allowing the generics industry to make an informed decision as to why, when and how an API or DP or related reagents/solvents, equipment and excipients should be evaluated for nitrosamines.

The generics industry proposes a risk-based approach to evaluate the possibility of nitrosamines in certain situations as provided below. Decision trees based on these scenarios are provided in Attachment A for API and Attachment B for DP.

The following will be taken into consideration with reference to API:

- When any inorganic or organic nitrite is used in any step of the manufacturing process of an API, an extensive evaluation should be done for all possible nitrosamines based on the starting materials, reagents and solvents in all the subsequent steps of the manufacturing process. If the nitrite is used upstream in the manufacturing process, steps will be taken to ensure that it is efficiently “washed out” to prevent nitrosation reactions from occurring downstream.
- When a drug has a secondary or tertiary amine or an N-alkyl amide, N-alkyl carbamate or N-alkylurea in its structure or any of the intermediates or impurities in the API have these structures, the formation of corresponding nitrosamines will be investigated during the manufacturing process development, even if there is no obvious source of nitrite (as we know, nitrites are ubiquitous and oxides of nitrogen, which are environmental pollutants, can also affect nitrosamine formation). Also, when the nitrosamines are found to be possible in the API or DP, they should be monitored on a regular basis in the API and/or DP as the risk in these cases are considered high.
- When solvents or reagents such as DMF (dimethylformamide), DMA (dimethylacetamine), DEA (diethylacetamide), DIPEA (diisopropylethylamine), morpholine (MOR), N-methyl-morpholine (NMM), pyrrolidine (PYR), or piperidine (PIP) are used in the manufacturing of an API, the sponsor would look for the corresponding nitrosamines. The incoming lots of all such solvents should be tested for the commonly occurring nitrosamines. If these amines are present in the DP based on their use in the API or excipients, a risk-based analysis is proposed to understand the possibility of the nitrosamines being formed in the DP. The risk in these cases may be considered medium or low and addressed based on vendor validation, skip testing and pharmaceutical development studies, which could demonstrate that the levels of the solvents in the DP do not carry the risk of nitrosamine formation.

- The generics industry would exercise caution related to recycling of solvents and, for certain cases, test recycled solvent for possible volatile nitrosamines.
- When any reagent used in the manufacturing of the API has a secondary, tertiary amine, or quaternary ammonium structure or could have a secondary or tertiary amine impurity, sponsors will look for nitrosamines related to these amines. There needs to be understanding of the manufacturing of the reagents. For example, tributyltin chloride shows traces of NDMA based on the fact that DMF is commonly a solvent used in its manufacturing process. In these cases, there may be vendor qualification process in place to assure that the incoming lot(s) of the reagents have been evaluated for possible presence of nitrosamines. For reagents considered high risk, the incoming lots will be tested to assure the absence of nitrosamines.
- N-alkylated amides, carbamates, and urea can be nitrosated. So, for reagents—starting materials with these structures—there is a possibility of nitrosamines being formed based on reaction conditions. In case these are used as reagents, the incoming lot(s) will be tested for the corresponding nitrosamines.
- When secondary and tertiary amines, N-alkyl derivatives of amides, carbamates, or urea generated as intermediates in the synthetic scheme of the API, these will be tested for the corresponding nitrosamines.
- If a Regulatory Starting Material (RSM) is downstream in a manufacturing process and supplied by an external vendor, a risk analysis related to presence of nitrosamines will be performed based on the structure of the RSM, manufacturing process and reagents used. The vendor should be able to provide information regarding how they control the nitrosamines in their RSM.
- If the API has nitrosamine as a process impurity, it will be controlled in the API and, if needed, in the DP. Also, attempts will be made by the API manufacturer to modify the process as a part of continuous development to eliminate the nitrosamine or lower its level to an acceptable limit.
- Assessment of the foregoing aspects of API manufacturing will identify processes wherein a nitrosamine could, theoretically, be introduced or generated in a manufacturing process. In some cases, sensitive and specific analytical methods

may be required to confirm the presence or absence of particular nitrosamines. However, for the preponderance of manufacturing processes that have a theoretical risk of nitrosamine presence, the alternative approaches, such as purge factor analysis, may be used to determine if the magnitude of risk warrants direct analytical testing.^{34,35,36}

The following will be taken into consideration with reference to DP:

- DP manufacturers who purchase API from an outside source will provide a questionnaire to the API supplier to ascertain whether the API has been adequately evaluated for nitrosamines. The responses provided by the API supplier will allow the DP manufacturer to better assess and determine if further testing is required of the DP for nitrosamines. An example of the questionnaire is provided in Attachment C.
- Request the excipient suppliers provide responses to the questionnaire created by IPEC Europe related to nitrosamines in excipients. The IPEC questionnaire is provided in Attachment D. Industry will also assess the risk of nitrosamines in the formulation arising from the API-excipient and excipient-excipient interaction.
- If nitrosamines are present in the API and excipients as process impurities based on the information from the vendors, perform a risk analysis related to the acceptability of the amount of nitrosamine that could be present in the DP to determine next steps at appropriately controlling the nitrosamine.
- If a nitrosamine is a degradant or there are residual amines in the API or any excipient, or there are amine degradants, the DP may need to be tested for the

34 Andrew Teasdale, Simon Fenner, Andrew Ray, Agnes Ford, and Andrew Phillips; A Tool for the Semiquantitative Assessment of Potentially Genotoxic Impurity (PGI) Carryover into API Using Physicochemical Parameters and Process Conditions; *Organic Process Research & Development*, **2010**, 14 (4), 943-94, doi: 10.1021/op100071n

35 Andrew Teasdale,* David Elder, Sou-Jen Chang, Sophie Wang, Richard Thompson, Nancy Benz, and Ignacio H. Sanchez Flores; Risk Assessment of Genotoxic Impurities in New Chemical Entities: Strategies To Demonstrate Control; *Org. Process Res. Dev.* 2013, 17, 11, 221–230. <https://dx.doi.org/10.1021/op300268u>

36 Barber C, Antonucci V, Baumann JC, et al. A consortium-driven framework to guide the implementation of ICH M7 Option 4 control strategies. *Regul Toxicol Pharmacol.* **2017**, 90, 22-28. doi:10.1016/j.yrtph.2017.08.008

corresponding nitrosamines. Based on the structure of the API and also the excipients, a science-based decision should be made if there is need to monitor the nitrosamines during the life cycle or based on medium level of risk and appropriate control of the reactants, a skip testing may suffice.

- With the packaging materials for DPs, including those composed of rubber or other elastomers, nitrocellulose should be taken into consideration in overall risk assessment related to nitrosamines in the DPs. Rubber or other elastomeric products may contain several nitrosamines like NDMA, NDEA, NDBA, NDBzA, and NMOR¹⁰. Nitrocellulose in lidding foils may react with amines available from printing ink or other sources to product nitrosamines²⁵. Based on the nature of the packaging components, a decision will be taken regarding the control of possible nitrosamines.

Extraneous sources of nitrosamines in API and DP:

- The industry will also evaluate the possibility of nitrosamines formed from the detergents used for cleaning the manufacturing equipment and include adequate controls if needed.
- The industry will evaluate the source of potable water, which could be used in the manufacturing of the API or any activity related to the DP to make sure that it meets the drinking water standards of the appropriate agencies (for example, WHO, EPA). This is to assure it does not have any nitrosamines or nitrites, which can be precursors for nitrosamines.

Analytical method related to analysis of nitrosamines:

- The sensitivity and reliability of analytical methods related to detection and quantitation of nitrosamines in pharmaceuticals is crucial due to the extremely low levels of these impurities determined acceptable by regulatory agencies. FDA has published methods including GC/MS-Head Space Analysis and LC-HRMS for detection of some of the familiar nitrosamines^{27,28}.
- The generics industry intends to use the analytical methods recommended by FDA appropriately to analyze the APIs and DPs. However, due to differences in the formulations and possibility of a particular analytical method not being

adequate for analysis of all possible volatile and non-volatile nitrosamines, new methods should be developed and considered. For instance, there are possibilities of artifacts from excipients and other sources that could be misconstrued as nitrosamines, based on a particular method. Thus, once a nitrosamine is detected in an API or DP, the sponsors will confirm its presence unequivocally based on orthogonal methods and control studies to determine the need for additional action based on their analysis that establishes the presence of nitrosamines.

Life Cycle Management:

- The original risk assessment related to the API or DP will be revisited in the event of changes that have the potential to modify the risk profile of the product. Some examples of changes that may entail re-evaluation of the risk profile are provided below:
 - For APIs, a change in the source of RSM, change in the source of solvents (for example, the decision to use recycled solvents), changes in the process that may incorporate risk of nitrosamines, changes in the reagents or solvents and any other change that may be relevant to levels of nitrosamines in the API.
 - For DPs, a change in the source of API, excipients, reformulation of the finished dosage form, changes in packaging that may incorporate higher risk of nitrosamines, changes in the process and any other changes that could impact the levels of nitrosamines in the drug product.

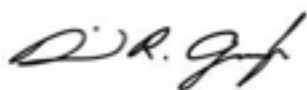
Conclusion

The generics industry commits to taking proactive steps to ensure the quality of generic medicines meets the highest safety standards determined by the FDA. The generics industry is eager to work with FDA to adopt a balanced risk-based approach to addressing the nitrosamine issue. We request the FDA revisit and potentially reassess the set safety limits of the common nitrosamines in pharmaceuticals based on new developments from recent studies, such as consideration for the duration, acute to chronic, use of a product.

The generics industry stands ready to work with the FDA so that we can strike the right balance, that of quality and safety. Further we stand ready to work with the FDA to mitigate creating or potentially exasperating unintended consequences, such as drug shortages, process improvements that are overly burdensome and unsustainable for the FDA and industry, as we refine risk-based approaches to better manage the concerns nitrosamines present.

AAM appreciates the opportunity to share our member companies collective thinking on how the generics industry can work with the agency to address the concerns around nitrosamines.

Sincerely,

A handwritten signature in black ink, appearing to read "D.R. Gaugh".

David R. Gaugh, R.Ph.
Senior Vice President for Sciences and Regulatory Affairs

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