2. a survey of individuals providing care for children under the age of 13 in a residential setting (Home-based Provider Interview) including individuals appearing on state and national lists of ECE providers (listed) and individuals not appearing on such lists (unlisted),

3. a survey of center-based ECE providers offering care for children age 5 years and under, not yet in kindergarten, in a non-residential setting (Center-based Provider Interview), and

4. a survey conducted with individuals employed in center-based ECE programs working directly with children in classrooms serving children age 5 years and under, not yet in kindergarten (Workforce Interview).

The household, home-based provider, and center-based provider surveys will require a screener to determine eligibility for the specific survey.

The 2024 NSECE data collection efforts will provide urgently needed information about the use and supply of ECE available to families across all income levels, including providers serving low-income families of various racial, ethnic, language, and cultural backgrounds, in diverse geographic areas. The household data will include characteristics of households with children under age 13, such as parental employment status and schedules, preferences and choices of non-parental care, and other key factors that affect their need for and access to ECE. The provider data will include home-based or center-based ECE providers (*e.g.,* private, non-profit, Head Start-funded, state or local Pre-K, or based in public schools) that do or do not participate in the child care subsidy program, and are or are not regulated, registered, or otherwise appear in state or national lists. Accurate data on families with young children and the availability and characteristics of ECE providers are essential to assess the current and changing landscape of ECE since the 2019 NSECE data collection, and to provide insights to advance policy and initiatives in the ECE field. The two previous rounds of NSECE, collected in 2012 and 2019, produced critical data about providers of ECE services, the ECE workforce, and families' needs and use of child care throughout the U.S. that remain unmatched by other data sources available.

Respondents: Households with resident children under age 13, home-based ECE providers serving children under age 13 (listed and unlisted), center-based ECE providers serving children age 5 and under (not yet in kindergarten), and classroom-assigned instructional staff (workforce) members working with children age 5 and under (not yet in kindergarten) in center-based ECE programs.

ANNUAL BURDEN ESTIMATES

Instrument	Number of respondents (total over request period)	Number of responses per respondent (total over request period)	Avg. burden per response (in hours)	Total/annual burden (in hours)
Household Screener (screening only)	62,758	1	.1	6,276
Household Questionnaire (no screener)	10,000	1	1	10,000
Home-based Provider Screener (screening only, listed home-based providers)	2,064	1	.03	62
Home-based Provider Questionnaire including screener (listed home-based providers)	4,360	1	.67	2,921
Home-based Provider Questionnaire, including screener (unlisted home-based providers)	1,158	1	.33	382
Center-based Provider Screener (screening only)	10,050	1	.1	1,005
Center-based Provider Questionnaire, including screener	8,392	1	.75	6,294
Workforce (Classroom Staff) Questionnaire	7,418	1	.33	2,448

Estimated Total Annual Burden Hours: 29,388.

Authority: Child Care and Development Block Grant Act of 1990 as amended by the CCDBG Act of 2014 (Pub. L. 113–186). Social Security Act 418 as extended by the Continuing Appropriations Act of 2017 and the TANF Extension Act of 2019. Section 3507 of the Paperwork Reduction Act of 1995, 44 U.S.C. chapter 35.

Mary B. Jones,

ACF/OPRE Certifying Officer.

[FR Doc. 2023–09455 Filed 5–3–23; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2023–N–1585]

Identification, Assessment, and Control of Nitrosamine Drug Substance-Related Impurities in Human Drug Products; Establishment of a Public Docket; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; establishment of a public docket; request for comments.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing the establishment of a docket to solicit public comments on the identification, assessment, and control of N-nitrosamine (nitrosamine) drug substance-related impurities (NDSRIs) that may be considered by the Agency in its regulation of these types of impurities in drug products. This notice identifies scientific and regulatory considerations regarding the identification, assessment, and control of NDSRIs, including areas that may benefit from collaborative efforts, and requests comments on these topics. This notice is not intended to communicate FDA's regulatory expectations on these issues but is instead intended to seek input from the public to inform scientific and/or regulatory approaches as appropriate.

DATES: Either electronic or written comments must be submitted by July 3, 2023.

ADDRESSES: You may submit comments as follows. Please note that late,

untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of July 3, 2023. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked, and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–FDA–2023–N–1585 for ''Identification, Assessment, and Control of Nitrosamine Drug Substance-Related Impurities in Human Drug Products; Establishment of a Public Docket; Request for Comments.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: Jason Bunting, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6366, Silver Spring, MD 20993–0002, 301–796–1292, *Jason.bunting@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

A. Nitrosamines, Including NDSRIs, in Human Drug Products

FDA has been investigating the presence of nitrosamine impurities in certain drug products since June 2018. Nitrosamines are common in water and foods, including cured and grilled meats, dairy products, and vegetables. Nitrosamines may increase the risk of cancer if people are exposed to them above acceptable levels. The acceptable intake (AI) limit is a level that approximates an increased cancer risk of one additional case in 100,000 people based on a conservative assumption of daily exposure to the impurity or impurities over a lifetime (70 years) (See FDA guidance for industry ''Control of Nitrosamine Impurities in Human Drug Drugs'' (Nitrosamine Guidance) at 10, available at *https://www.fda.gov/media/141720/download* (Ref. 3).

When FDA was informed of the presence of an impurity identified as N-nitrosodimethylamine (NDMA) in valsartan, an angiotensin II receptor blocker (ARB), it began an investigation in which it 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 voluntarily recalled the affected batches of these drug products, which led to a drug shortage in some of the affected products. In addition, FDA evaluated processes used in synthesis of the active pharmaceutical ingredient (API) and learned that common synthetic pathways could also introduce other types of nitrosamine impurities besides NDMA. FDA has continued to learn of the existence of nitrosamine impurities such as NDMA in drug products in several drug classes (see Ref. 3 at 2–3).

FDA originally published the Nitrosamine Guidance on September 3, 2020 (85 FR 55017), and updated the guidance on February 24, 2021 (Ref. 3). The guidance provides recommendations for industry regarding nitrosamines, and NDSRIs are a subcategory of these impurities that share structural similarity with the active pharmaceutical ingredient in drug products. In the Nitrosamine Guidance, FDA recommends manufacturers of APIs and drug products should take steps to detect and prevent unacceptable levels of nitrosamine impurities in drug products, or avoid their presence when feasible.[1] Specifically, FDA

[1] The Nitrosamine Guidance notes that new drug application (NDA) and abbreviated new drug application (ANDA) holders or applicants, drug master file 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 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 the Nitrosamine Guidance. This applies to drug products currently available on the

recommends a three-step process that manufacturers should take to mitigate nitrosamine impurities in their products: (1) conduct risk assessments for nitrosamines in their products; (2) conduct confirmatory testing if risks are identified; and (3) report changes implemented to prevent or reduce the presence of nitrosamine impurities in drug products in approved and pending new drug applications (NDAs) and abbreviated new drug applications (ANDAs). The Nitrosamine Guidance describes some conditions that may introduce or create nitrosamine impurities (a nitrosating reaction between secondary, tertiary, or quaternary amines and nitrous acid (nitrite salts under acidic conditions)) and provides FDA-recommended AI limits for six nitrosamine impurities that could be present in drug products (see Ref. 3 at 10).

More recently, and often in response to the risk assessment recommended in the Nitrosamine Guidance, FDA has received an increasing number of reports of certain types of nitrosamine impurities that have formed in drug products across multiple drug classes. These NDSRIs are a class of nitrosamines sharing structural similarity to the API, and thus, differ in certain respects from small molecule nitrosamine impurities (*i.e.,* nitrosamine impurities that do not share structural similarity to the API, and are therefore, not considered NDSRIs) identified in the Nitrosamine Guidance (see Ref. 3 at 10). NDSRIs can be generated during manufacturing, or during the shelf-life storage period of the drug product. They can also be generated during the synthesis of the drug substance. In some cases, the root cause of NDSRI formation has been attributed to nitrite impurities present in excipients at parts-per-million amounts. Nitrite impurities have been observed in a range of commonly used excipients (as well as water) and may lead to the formation of NDSRIs in certain drug products. In general, there is a risk of generating nitrosamine impurities when nitrites are in the presence of secondary, tertiary, or quaternary amines. Secondary or tertiary amines are known to be part of the chemical structure of several hundred APIs. Accordingly, depending on the formulation and manufacturing process for the drug product, as well as ongoing oversight of the quality of materials produced by suppliers, there may be a risk of nitrosamine formation in a substantial number of drug products.

In November 2021, FDA alerted the public regarding the presence of NDSRIs and indicated that manufacturers could ascertain the presence of NDSRIs using the same three-step process identified in the Nitrosamine Guidance (Ref. 4). As discussed further below, FDA also conveyed possible mitigation strategies, and encouraged applicants to develop control strategies or design approaches to reduce NDSRIs to acceptable levels or eliminate them (where feasible).

NDSRIs present unique scientific and regulatory challenges for FDA because each NDSRI is unique to the API, and there is limited compound-specific data that is available to inform safety assessments. Additionally, design of validated test methods for identification of NDSRIs and modification of existing test methods for assessment of their mutagenic potential may raise novel scientific considerations.

B. Safety Assessments of the Potential for Mutagenic and Carcinogenic Risk

In the Nitrosamine Guidance, FDA recognizes that nitrosamine compounds are potent genotoxic agents in several animal species, and some have been classified as probable or possible human carcinogens by the World Health Organization's International Agency for Research on Cancer (see Ref. 3 at 5). The framework for identifying, categorizing, qualifying and controlling DNA reactive (mutagenic) impurities to limit potential carcinogenic risk is provided in FDA and International Council for Harmonisation guidance for industry entitled ''M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk'' (ICH M7(R1) Guidance), available at *https://www.fda.gov/media/85885/download* (Ref. 5). (The ICH M7(R1) Guidance was prepared under the auspices of the ICH). Nitrosamines as a structural group are referred to as ''cohort of concern'' compounds in the ICH M7(R1) Guidance because of their classification as high-potency mutagenic carcinogens. It is currently unknown if all or some NDSRIs are associated with this classification.

The ICH M7(R1) Guidance provides guidance to derive AI limits for some chemicals that are considered mutagens and carcinogens and are also commonly used in the synthesis of pharmaceuticals or are useful examples to illustrate the principles for deriving compound-specific intakes otherwise described in the ICH M7(R1) Guidance (see the **Federal Register** notice issued March 14, 2018 (83 FR 11210). Specifically, the ICH M7(R1) Guidance recommends applicants use a hazard assessment, which involves an initial analysis of actual and potential impurities by conducting database and literature searches for carcinogenicity and bacterial mutagenicity data, to classify impurities into one of five classes and proposes action for control based on the resulting class (with Class 1 being known mutagenic carcinogens and Class 5 being impurities with no structural alerts,[2] or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity) (see Ref. 5 at 10). If data are not available for such a classification, a computational toxicology assessment should be conducted using two (quantitative) structure-activity relationship ((Q)SAR) methodologies that can predict the outcome of a bacterial mutagenicity test (see Ref. 5 at 9–10). In the ICH M7(R1) Guidance, FDA recommends that impurities for each class be controlled at specified limits; for example, it recommends Class 1 impurities be controlled at or below compound-specific acceptable limits, and Class 5 impurities be controlled as non-mutagenic impurities (see Ref. 5 at 10).

1. Assessment of Potential Mutagenicity and Carcinogenicity

FDA typically requests that applicants assess the potential for an impurity to be mutagenic by conducting a standard in vitro bacterial reverse mutation test (Ames test). If this in vitro mutagenicity testing is negative for a nitrosamine impurity, FDA has requested further testing because standard methods used for the Ames test may not be adequate to characterize the mutagenic potential of nitrosamines, in some cases producing negative results with known mutagenic nitrosamines. Information in published scientific literature suggests that some Ames tests (*e.g.,* those conducted with rat S9) may not be sensitive enough to assess the mutagenicity of nitrosamine compounds because of species-specific differences in metabolic activation of potential mutagens. Additionally, there is limited experience on the sensitivity of these tests for NDSRIs, which are more complex structures than the more commonly identified nitrosamines in the Nitrosamine Guidance. Therefore, FDA's National Center for Toxicological Research has been testing different conditions to develop an enhanced

U.S. market as well as those with pending applications. See Ref. 3 at 1, footnote 3. Holders of biologics license applications for biological products that contain chemically synthesized fragments or biologic-led combination products that contain a drug constituent part also may be affected.

[2] The ICH M7(R1) Guidance defines a structural alert in the context of the guidance as ''a chemical grouping or molecular (sub) structure which is associated with mutagenicity'' (Ref. 5 at 129).

Ames test that is intended to provide a more reliable assessment of potential mutagenicity in small molecule nitrosamine impurities and NDSRIs.

In some circumstances in which the results of an enhanced Ames test are negative, the mutagenic potential of the impurity was further assessed in an in vivo transgenic gene mutation test to confirm the in vitro findings. If further in vivo testing is to be conducted, the selection of the in vivo mutagenicity tests should be scientifically justified based on knowledge of the mechanism of action of the impurity and expected target tissue exposure (see Ref. 5 at 11 and at (Note 3) 21–22). To avoid potentially duplicative nonclinical in vitro or in vivo testing of NDSRIs by manufacturers of drug products containing the drug substance, FDA is interested in exploring the feasibility of collaborative efforts among applicants and manufacturers of affected drug products.

2. Computational Toxicology

In general, (Q)SAR models are accepted as a scientific tool for predicting and classifying the biological activities of untested chemicals. A computational toxicology assessment using (Q)SAR methodologies can predict, with acceptable confidence, the outcome of an Ames test by using two complementary, validated modeling methodologies (statistical-based and expert rule-based) and can be used to classify an impurity as mutagenic or non-mutagenic (see Ref. 5 at 10). The methodology uses statistical and/or manual approaches to correlate and rationalize variations in the biological activity of a series of chemicals with variations in their molecular structures, which are often represented by a set of quantities commonly known as ''structural descriptors.'' Because (Q)SAR models can generate a prediction of a chemical's biological activity from structural descriptors more rapidly than in vitro or in vivo testing can be conducted, they provide a means to efficiently assess nitrosamine toxicity when experimental data are unavailable. However, the predictive performance of (Q)SAR models depends on many factors, particularly on the quality of biological training data, descriptor selection, and modeling algorithm. Therefore, FDA has been working with model developers and stakeholders to advance predictive toxicology, with a focus on the use of (Q)SAR methodologies in assessing potential mutagenicity and carcinogenicity of NDSRIs.

3. Determining AI Limits for NDSRIs

A recommended AI limit is based on a safety assessment that includes evaluation of the mutagenic and carcinogenic potential of the impurity and represents the level at or below which FDA has determined that the impurity or impurities would not pose a safety concern for patients taking the drug product. The AI limit is a level that approximates an increased cancer risk of 1:100,000 based on a conservative assumption of daily exposure to the impurity or impurities over a lifetime (70 years) (see Ref. 3 at 10 and Appendix B ''FDA Determination of Acceptable Intake Limits''). The AI limit is generally described in nanograms per day, and each applicant establishes specifications to control for the level of impurity or impurities in their drug products (in parts per million) based on the maximum daily dose of the drug product under the labeled conditions of use. Once a recommended AI limit has been established, applicants and manufacturers would generally be expected to control impurities within the recommended AI limit (see Ref. 3 at 14, 15). Applicants or manufacturers should contact FDA regarding drug products with unacceptable levels of nitrosamine impurities that are already in distribution (see Ref. 3 at 14, 15). Additionally, applicants and manufacturers may need to modify the manufacturing processes or reformulate their drug products to control impurities within the recommended AI limit [3] or submit additional testing to FDA that would demonstrate the applicant's proposed limit is safe.[4]

Calculating a recommended AI limit for NDSRIs is often more challenging than calculating recommended AI limits for small molecule nitrosamines, primarily because NDSRIs are unique to each API and there is usually limited or no existing safety data (*e.g.,* rodent carcinogenicity data) on NDSRIs (see also Ref. 5 at 12 and note 4 on calculating a compound-specific AI limit). FDA has published recommended AI limits for a limited number of NDSRIs, but unlike more commonly known nitrosamines (such as those identified in the Nitrosamine Guidance), a recommended AI limit has not yet been determined for most NDSRIs.

If mutagenic potential is identified through toxicological testing or computational toxicology models, FDA and applicants have used (Q)SAR methods to identify and select a data-rich surrogate that is similar in structure and reactivity to the data-poor NDSRI to generate an estimate of carcinogenic potency from which an AI limit can be determined. In this scenario, surrogates are compounds containing an N-nitroso structural alert in the same chemical environment as an NDSRI and for which robust carcinogenicity data are available (see Ref. 5 at 11–12). The rationale for the choice of surrogate (similar in structure and reactivity) is significant because test data from the identified surrogate is then used to generate an estimate, either quantitatively or qualitatively, for the data-poor compound (commonly referred to as a ''read-across analysis'').

The nitrosamine structural alert environment is an important factor when selecting appropriate reference compounds for a read-across analysis and may include consideration of the degree of substitution, steric bulk, electronic influences, potential for metabolic activation, stability/reactivity of the resulting metabolites, and overall molecular weight. Additionally, the quality of carcinogenicity studies in the published scientific literature can be quite variable; however, 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 (see Ref. 5 at 36).

C. FDA's Ongoing Work on Nitrosamine Risk Assessment and Mitigation

Since the issuance of the Nitrosamine Guidance, FDA has continued to work to better understand the root causes of nitrosamines, develop mitigation strategies that can eliminate or minimize the presence of nitrosamines in drug products, and improve approaches to risk assessment (mutagenicity and carcinogenicity) of NDSRIs in drug substances and drug products that can inform recommended AI limits.

As FDA learned more about NDSRI formation and received increasing numbers of reports from industry on the presence of NDSRIs, the Agency identified on its web page two examples of mitigation strategies related to formulation design to assist

[3] For recommendations to API manufacturers and drug manufacturers see Ref. 3 at 11–15.

[4] See, *e.g.,* generally Ref. 5, which provides a framework for the identification, categorization, qualification, and control of mutagenic impurities to limit potential carcinogenic risk, at 4 and ''Table 1: Impurities Classification With Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions,'' at 10. The guidance further explains that if an impurity has a positive bacterial mutagenicity result and cannot be controlled at an appropriate acceptable limit, then it may be recommended that the impurity be tested in an in vivo gene mutation assay, which may support recommending a compound-specific impurity limit (see Ref. 5 at 11).

manufacturers in reducing the levels of NDSRIs in drug products. One mitigation strategy was derived from published literature reports that demonstrated that commonly used antioxidants, such as ascorbic acid (vitamin C) or alpha-tocopherol (vitamin E), inhibit the formation of nitrosamines in vivo, based on data from human gastric fluid in vitro studies (see Ref. 4). FDA advised that recent work preliminarily demonstrated that the addition of these antioxidants to formulations may significantly inhibit the formation of NDSRIs in drug products. FDA also presented a second possible mitigation strategy related to formulation design based on the fact that the formation of nitrosamines typically occurs under acidic conditions, whereas, in a neutral or basic environment, the kinetics of these reactions are significantly reduced (Ref. 4). FDA has encouraged manufacturers to consider these as well as other innovative strategies to reduce the formation of NDSRIs to acceptable levels in drug products.

D. Regulatory Challenges

The identification of a new impurity, such as an NDSRI, may have implications for a cohort of pending or approved NDAs (including applications submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)(2))) and ANDAs and also creates unique challenges from a regulatory perspective. For example, a generic drug applicant typically may qualify the level of an impurity that does not have a limit in an applicable U.S. Pharmacopeia monograph or that does not otherwise have a recommended AI limit (*e.g.,* as described in applicable guidance) by comparing its proposed product to the observed amounts of the impurity in the previously approved drug product (the reference listed drug) on which it relies for approval (see Refs. 1 and 2). This approach reflects that identification and evaluation of certain impurities to establish the biological safety of the impurity at the level(s) present in the API or drug product typically occurs before approval of the NDA for the reference listed drug, and subsequently, ANDA applicants can conduct comparative testing of their products and the reference listed drug to qualify impurities. However, challenges arise when each applicant in a cohort of pending or approved NDAs (including section 505(b)(2) applications) and ANDAs concurrently conducts risk assessments for the presence of an NDSRI in their drug products and, if present, develops data to support an AI limit and specifications for controlling the impurity in their drug products.

Moreover, information on impurities in drug products that may reveal an aspect of an applicant's manufacturing method or process generally has been protected from public disclosure, unless such information has been previously disclosed by the applicant or is otherwise publicly available. Thus, FDA may be limited in the impurity information that it can disclose to facilitate efficient evaluation of other products and to inform applicants of actions they can take to mitigate nitrosamine risk. In addition, there are considerations that may constrain FDA's ability to disclose certain information provided by an applicant in FDA's evaluation of other applicants' submissions to FDA, which can lead to potentially duplicative nonclinical tests (which may include animal testing) to characterize the risk and inform a recommended AI limit. This can be a significant concern when a newly identified NDSRI may have implications for a cohort of pending or approved marketing applications. For example, there are circumstances in which potential constraints regarding disclosure could hamper FDA's ability to quickly and publicly identify a compound-specific recommended AI limit for an NDSRI that may be applicable to all drug products that contain the API. Potential constraints related to disclosure of certain information regarding impurities could also lead to delays in providing applicants, including follow-on and generic drug products, with information to develop drug products with acceptable impurity profiles. Additionally, uncertainty about the presence and/or acceptability of the level of an impurity raises additional regulatory challenges and could lead to some applicants conducting unnecessary studies or even discontinuing drug products from the market, potentially resulting in drug shortages. These difficulties can impact patient access to medications, including drugs that are considered medically necessary.

To avoid these potential issues, at times, FDA generates and makes publicly available information or research to support the development of recommended AI limits by conducting additional studies, developing enhanced Ames testing, or using (Q)SAR methodology to identify appropriate surrogates from which read-across can be used to estimate carcinogenic potency. Applicants can use this FDA-generated information to set individual drug product specifications. The absence of publicly available data to support a recommended AI limit for an NDSRI can result in potentially duplicative studies to support a recommended AI limit. Moreover, if in vivo animal studies are necessary to assess the risk of a particular NDSRI, such potentially duplicative testing may not align with FDA's policy to replace, reduce, and refine the use of animals for safety testing (the 3R principles), where possible (see, *e.g.,* Ref. 6 at 1).

E. Collaborative Efforts To Develop NDSRI Data

FDA has encouraged collaborative efforts by applicants and other stakeholders, together with the Agency as appropriate, to help address the challenges presented by NDSRIs. FDA also has collaborated with international regulatory agencies through the Nitrosamines International Strategic Group and the Nitrosamines International Technical Working Group, which were formed to share scientific knowledge and current thinking on technical safety and quality topics related to nitrosamines and to promote technical convergence among member jurisdictions, where possible. In other areas, FDA is collaborating on multi-laboratory projects being organized by the Health and Environmental Sciences Institute's Genetic Toxicology Technical Committee that include industry stakeholders and regulatory agencies such as Health Canada and European Medicines Agency. Additionally, FDA has been actively engaged with model developers and stakeholders to advance predictive toxicology with a focus on the use of (Q)SAR methodologies in assessing potential mutagenicity and carcinogenicity of NDSRIs.

Development of laboratory test methods to identify NDSRIs is an area that could benefit from collaborative efforts. In the Nitrosamine Guidance, FDA encourages manufacturers or laboratories to make validated test methods publicly available (*e.g.,* by posting on the method developer's website) to facilitate faster testing of other similar drug products. FDA also accepts requests to post privately developed methods on FDA's website if FDA's review of the method protocol finds it scientifically sound and if the method owner provides written authorization for posting by FDA (see Ref. 3 at 11, footnote 37). As another example, a positive bacterial mutagenicity result may warrant an additional in vivo gene mutation assay, typically a transgenic mutation assay, to understand the relevance of the bacterial mutagenicity test under in vivo conditions (see Ref. 5 at 11 and (Note 3)

(identifying the transgenic mutation assay as appropriate for followup for any positive bacterial mutagenicity test as opposed to other tests, which are recommended under more limited circumstances). When such in vivo testing is warranted, industry collaboration on the testing to develop robust data and share results among themselves could enhance scientific analyses and could facilitate regulatory decision-making. Similarly, we have encouraged applicants to publish scientific research and test results to further scientific knowledge on NDSRIs and facilitate regulatory decision-making, as appropriate.

II. Issues for Consideration and Request for Comments

FDA is requesting comments from the public regarding the identification, assessment, and control of NDSRIs in drug product development and regulatory review to provide interested parties an opportunity to comment on scientific and regulatory considerations, including areas that may benefit from collaborative efforts. FDA is also interested in any challenges preventing industry from identifying, assessing, and controlling NDSRIs that may assist FDA in its analysis.

The questions posed below are not meant to be exhaustive. FDA is interested in other pertinent information that stakeholders would like to provide on issues and challenges related to addressing NDSRIs. FDA is particularly interested in comments on the following topics:

A. General Questions

1. What additional topics related to the evaluation of nitrosamines should be a priority for the Agency to address through guidance documents?

2. What factors should FDA consider in prioritizing its evaluation of NDSRIs on a compound-specific basis?

3. What additional mitigation strategies should be considered for reducing NDSRI formation or eliminating these impurities (where feasible)?

B. NDSRI Risk Assessment

1. What scientific and technical factors should FDA consider in developing best practices for conducting testing for NDSRIs (*e.g.,* Ames test, enhanced Ames test, followup in vitro mutagenicity, in vivo transgenic gene mutation test) in support of establishing AI limits?

a. Are there other tests recommended for assessing mutagenic potential of NDSRIs, and how supportable are these methods?

b. Would ''short-term'' carcinogenicity testing (*e.g.,* 6-month transgenic mouse model) be informative to evaluate the risk associated with NDSRIs?

c. If so, what are the advantages and disadvantages to such testing?

d. Are there other types of studies that may further inform FDA about the risk associated with NDSRI (*e.g.,* in vitro/in vivo metabolism, DNA biomarkers, identification of reactive intermediates)?

2. FDA recommended in the Nitrosamine Guidance that confirmatory testing of drug products and submission of required changes in drug applications be concluded on or before October 1, 2023 (see Ref. 3 at 17). Would an extension of the recommended timeline for submission of changes in drug applications as described in the guidance to June 1, 2024, allow for additional assessment of NDSRIs and enable collaborative efforts among affected applicants? How can FDA further support manufacturers' efforts toward completion of confirmatory testing?

C. Collaborative Efforts To Develop NDSRI Data and Establish and Implement Recommended AI Limits

1. How can FDA facilitate collaborative efforts to generate reliable compound-specific data on NDSRIs and reduce the need for additional and potentially duplicative testing?

2. Are there obstacles that industry has encountered when engaging in collaborative efforts that could allow companies to share data to assess the safety of NDSRIs, particularly with the intent of reducing redundant testing and integrating the 3R principles? Such examples of collaboration may include enhancing (Q)SAR methods and models, conducting in vitro mutagenicity testing and/or in vivo transgenic gene mutation tests. If there are such obstacles, are there ways that FDA could facilitate collaboration?

D. Establishing and Implementing Recommended AI Limits and Access to Medications

1. In implementing recommendations for controlling nitrosamines, including NDSRIs, have manufacturers or suppliers experienced difficulties with meeting recommended AI limits that has led to discontinuation of manufacturing or distribution?

III. References

The following references are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov.* FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

1. Food and Drug Administration (FDA) guidance for industry ''ANDAs: Impurities in Drug Substances,'' June 2009, available at *https://www.regulations.gov/document/FDA-1998-D-0021-0008.*

2. FDA guidance for industry ''ANDAs: Impurities in Drug Products,'' November 2010, available at *https://www.fda.gov/media/71351/download.*

3. FDA guidance for industry ''Control of Nitrosamine Impurities in Human Drugs,'' February 2021, available at *https://www.fda.gov/media/141720/download.*

4. FDA, ''Updates on Possible Mitigation Strategies To Reduce the Risk of Nitrosamine Drug Substance-Related Impurities in Drug Products,'' available at *https://www.fda.gov/drugs/drug-safety-and-availability/updates-possible-mitigation-strategies-reduce-risk-nitrosamine-drug-substance-related-impurities.* Last accessed April 14, 2023.

5. FDA and International Council for Harmonisation guidance for industry ''M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk,'' March 2018, available at *https://www.fda.gov/media/85885/download.*

6. FDA and International Council for Harmonisation guidance for industry, ''M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals'' January 2010, available at *https://www.fda.gov/media/71542/download.*

Dated: May 1, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. FDA–2022–N–1894; FDA–2018–N–3303; FDA–2022–N–0576; FDA–2022–N–1794; FDA–2011–N–0902; FDA–2009–N–0545; FDA–2016–N–2474; FDA–2010–D–0350; FDA–2012–D–0530; FDA–2016–N–2683; FDA–2013–N–0403; FDA–2013–N–0134; FDA–2022–N–2440; FDA–2013–N–0879; and FDA–2014–N–1048]

Agency Information Collection Activities; Announcement of Office of Management and Budget Approvals

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a