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Dockets Management Staff (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Identification, Assessment, and Control of Nitrosamine Drug Substance-Related Impurities in Human Drug Products; Establishment of a Public Docket; Request for Comments, 88 Fed. Reg. 28557, 28557-28562 (May 4, 2023); Docket No. FDA-2023-N-1585-0001.

The U.S. Food and Drug Administration (FDA or Agency) published a Federal Register notice on May 4, 2023, 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.

The Consumer Healthcare Products Association (CHPA)[1] thanks FDA for providing a process to give feedback from industry leveraging science and risk-based approaches to appropriately identify, assess and control (where needed) NDSRIs and preventing unacceptable levels of nitrosamines in drug products.

Members are facing challenges related to NDSRIs resulting in significant uncertainties in implementing control strategies and possible risk mitigation strategies. The following comments are provided below to address each FDA question posed including other pertinent information that CHPA members request FDA consider.

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

CHPA Comments:
CHPA members request the Agency to prioritize harmonization of global regulatory guidance. Specifically, CHPA members strongly urge the Agency to update the

[1] The Consumer Healthcare Products Association (CHPA) is an over 140-year-old national trade association representing the leading manufacturers and marketers of over-the-counter (OTC) medicines, consumer medical devices, and dietary supplements. CHPA is committed to empowering consumer self-care by preserving and expanding choice and availability of consumer healthcare products. www.chpa.org

current FDA Guidance for Industry *Control of Nitrosamine Impurities in Human Drugs* to align the control strategy for finished drug products, drug substances and/or intermediates to support global harmonization and consistency with the European Medicines Agency (EMA) and Co-ordination Group for Mutual Recognition and Decentralised Procedures – Humans (CMDh) *Questions and answers for marketing authorisation holders / applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral* to allow for exceptions from routine testing, provided the root cause of contamination is known, for example:

- If the amount of nitrosamine present is consistently below 10% of the acceptable limit based on Acceptable Intake (AI) in the API or in the finished product, then a test for the nitrosamine can be omitted from the specification.
- If levels of a single nitrosamine are consistently below 30% of the acceptable limit based on AI in the API or the finished product, skip-testing according to the ICH Q6A definition is acceptable.

Further, CHPA members request that FDA develop a process by which approved AI can be provided to industry in a timely manner, examples could include a stand-alone list accessible via FDA website or Q&A document that allows for rapid updating. For clarity, CHPA is requesting that FDA publish approved AI for industry and is not requesting that confidential or proprietary data/information that justified the AI be provided.

Additionally, CHPA requests FDA establish guidance on acceptance of a Weight of Evidence (WoE) approach to establish an AI, e.g., based on a combination of data sources such as read-across, enhanced Ames studies (i.e., designed to increase its sensitivity for the detection of nitrosamines, with the inclusion of a liquid pre-incubation phase and activation using induced hamster S9 and rat S9), structural features reducing likelihood of formation, structural features reducing potency, and metabolic profiling. Also, CHPA recommends FDA take a WoE approach (e.g., read-across, in-vitro data, structural considerations) to support a conclusion that a specific nitrosamine can be considered to be outside the Cohort of Concern such that the ICH M7 (R1) Threshold of Toxicological Concern (TTC) of 1.5 µg/day can be applied as well as other ICH M7 accepted practices (i.e., less-than-lifetime).

CHPA also requests FDA to update guidance for NDSRIs to reflect varying risk levels. The recent FDA/HESI Research Roadmap Planning on Hazard and Risk Assessment of Nitrosamine Impurities in Drugs workshop held May 31-June 1, 2023, provided data to support that not all NDSRIs fall within the Cohort of Concern; this has also been the subject of recent peer-reviewed literature (e.g., Ponting and Foster, 2023[1]). Therefore, CHPA member companies request that the guidance be revised to reflect this important distinction when specifying limits and applying the TTC approach as per ICH M7 and other accepted practices (i.e., less-than-lifetime). It is evident that a blanket approach to all NDSRIs may not be appropriate, as some substances do not pose significant concerns in terms of nitrosamine impurities. By acknowledging these variations in risk, the FDA can provide more targeted and

proportionate guidance, ensuring a more effective and efficient regulatory framework.

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

CHPA Comments:

CHPA encourages FDA to consider the potential for drug shortages for all types of drug products, including those sold over-the-counter (OTC) in its prioritization efforts. Additionally, applications that are pending should also be prioritized as the approval delays directly impact patients and consumers from getting needed medicines of either new products or generic products. CHPA also encourages the FDA to consider actual/realistic consumer exposure to drug (including OTC) products, particularly for those that are used only intermittently up to a few times per year.

Based on recent polling done across CHPA members, it was revealed that no member has yet received feedback from the FDA regarding a proposed AI. Several CHPA members have provided data and AI justification for NDSRIs well over a year ago and are still awaiting FDA feedback and lack clarity on what additional information FDA would require supporting the proposed AI. The FDA's significant lag in feedback does not allow industry to comply with guidance timing for mitigation or have the needed clarity on what mitigation activities might be required.

CHPA urges FDA to make the limit-setting process more transparent, e.g., provide visibility to NDSRIs (those related to both the API and impurities) that are under evaluation along with what information is needed to complete the review. CHPA is supportive of more engagement with industry through workshops and other forums through which the Agency can provide routine updates on NDSRIs under evaluation, what information is needed, and progress on studies being conducted or supported by FDA.

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

CHPA Comments:

As noted previously, CHPA strongly encourages that FDA guidance documents align with EMA guidance to outline criteria for when mitigation strategies may not be needed, e.g., when nitrosamine levels are consistently below thresholds that allow for routine testing exceptions or when a nitrosamine impurity is not part of the Cohort of Concern (CoC) based on WOE. In such cases, mitigation strategies need not be employed.

When mitigation strategies may be needed to reduce NDSRI formation, industry needs sufficient time to implement from the point that an AI is published. CHPA acknowledges FDA's recommendations on incorporating scavengers in formulation as a remediation strategy to *control nitrosamines*; however, we believe that a more comprehensive understanding of the time frame involved in such pharmaceutical development is necessary. As companies strive to meet regulatory requirements, it is crucial to factor in realistic timelines to ensure successful implementation and compliance. Considering the complex nature of pharmaceutical development and the various stages involved, it is vital to provide guidance that reflects the practical challenges faced by the industry. Incorporating a realistic time frame in the FDA's guidance would enable companies to allocate resources effectively, plan for necessary research and development, and navigate the regulatory landscape more efficiently.

Overall, mitigation strategies are likely to be complex requiring changes in suppliers and/or the formulation, both of which require proper development time including formula optimization, confirmatory screening, stability, and, in some cases, justification of new ingredients and post-approval submissions.

B. NDSRI Risk Assessment

FDA: 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, follow-up 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)?*

CHPA Comments:

The recent FDA/HESI Research Roadmap Planning on Hazard and Risk Assessment of Nitrosamine Impurities in Drugs workshop held May 31-June 1, 2023, provided much feedback to FDA on various methods that may be used to assess NDSRIs (both API and impurity related). However, through the testing and research done to date by several industry members and organizations, it is clear that a large amount of data is available, and we urge FDA and other regulators to gain access to

the various platforms of data so that guidance may be established for industry promptly regarding study protocols, WoE, and potentially classes of NDSRIs.

As noted previously, CHPA requests FDA to establish guidance on acceptance of a WoE approach to establish an AI, e.g., based on a combination of data sources such as read-across, Ames data from studies using optimized design to detect nitrosamines, structural features reducing likelihood of formation, structural features reducing potency, and metabolic profiling. As recently reported in the scientific literature, the Ames assay conducted under OECD 471 guideline is highly sensitive for detecting carcinogenic hazards of Nitrosamines (Trejo-Martin, et al., 2022[2]). Also, CHPA recommends FDA take a WoE approach (e.g., read-across, in-vitro data, structural considerations) to support a conclusion that the ICH M7 (R1) Threshold of Toxicological Concern (TTC) of 1.5 µg/day can be applied as well as other ICH M7 accepted practices (i.e., less-than-lifetime).

CHPA also requests FDA to continue to support the use of read-across data when available and properly justified, including such cases as described in ICH M7 which states "…studies that did not fulfill all of the above criteria [for robustness] were, in some cases, considered adequate for derivation of an AI when other aspects of the study were robust…" CHPA notes a manuscript on this topic, including case studies of nitrosamines, has been accepted for publication (Felter et al., accepted) and is expected to be publicly available in the near future.

Further, CHPA requests FDA to provide timely feedback and guidance on accepted read-across and Structure-Activity Relationship (SAR) approaches that can be implemented in lieu of traditional testing methods. In order to confidently apply these alternative approaches, clear guidance from regulatory authorities is essential. CHPA asks for FDA's expertise and guidance in establishing accepted frameworks and criteria for utilizing read-across and SAR methodologies for NDSRIs.

Also as noted previously, CHPA requests that FDA give consideration to actual/realistic consumer exposure to drug products such that the average daily dose can be considered for comparison to an AI rather than assuming an exposure to the maximum dose every day for a lifetime. This is particularly relevant to products that are only used occasionally by consumers and is consistent with the definition of an AI as described in the ICH guidance (i.e., an intake "considered to be protective for a lifetime of daily exposure"). Importantly, it is also consistent with the method used in the calculation of an AI based on the TD50 from a rodent cancer bioassay that does not involve daily lifetime (assumed to be 2 years) exposure. In such cases, the doses administered to the animals are adjusted to reflect the average daily dose prior to calculating the TD50. Thus, to make an appropriate comparison with a consumer exposure, a similar adjustment should be made to the consumer exposure with appropriately conservative assumptions.

FDA: 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?

CHPA Comments:

CHPA members request an extension to both Step 2 (confirmation testing) and Step 3 (mitigation activities) timelines. While an extension beyond the current deadline of October 1, 2023, will be helpful, a new deadline of June 1, 2024, is not expected to allow sufficient time to complete testing, collaborative efforts, as well as potential mitigation activities necessary to submit changes for NDSRIs. Currently, the Step 2 and Step 3 timeline for completion are the same and they should be separated to allow for proper testing as well as mitigation, when needed, to continue to support the availability of OTC drug products. Several CHPA members are continuing to experience testing challenges due to capacity and analytical method constraints based on known complexities, availability of reference standards, specialized instrumentation and trained experts required to achieve accurate results with appropriately low levels of detection. Further, as described previously, many members have submitted proposed AI for NDSRIs and are still waiting on FDA feedback. Mitigation (reduction or elimination) of an NDRSI may not be necessary if the root cause and actual levels are well understood and significantly less than the AI (e.g., < 10%). In many cases, mitigation activities require significant investment and time to support potential supplier changes, reformation activities, stability studies, and regulatory notifications. Industry is unable to make proper risk and scientific-based decisions on the extent to which mitigation is needed without feedback from FDA and/or published AIs for NDSRIs that have been submitted and more clarity on acceptance of WoE approaches.

CHPA requests FDA to share the NDSRIs (related to both API and impurities) that are under review with Agency so companies are aware and can avoid duplicating non-clinical testing. Additionally, FDA should not enforce a timeline for Step 3 for those NDSRIs until a limit is published and made available to industry.

Therefore, CHPA members propose that the Step 2 and Step 3 deadlines be separated and that the Step 3 timeline be established from the date that an AI is published rather than a default or arbitrary date set, such as June 1, 2024. It is further recommended that the Step 3 timeline is set to up to 3 years from the AI publication to allow for adequate root cause understanding, mitigation activities and setting of control strategies to ensure continued availability of OTC drug products.

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

FDA: 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?

CHPA Comments:

CHPA requests FDA to take a lead role in identifying areas where specific collaboration is needed around data gaps and what information is needed to fill the gap based on the data available thus far. CHPA urges FDA to gain access to existing data sharing forums (such as the Lhasa Complex Nitrosamines Consortium) and serve to create a central repository of data for regulator access to support guidance development, including WoE approaches. Additionally, CHPA requests FDA to provide timely feedback to industry on proposed NDSRIs, especially those where a read-across approach has been well-justified. Without clear direction, timely feedback and transparency in the process as described earlier, duplicative testing by industry, potential delays and/or the potential for deriving different AIs risks will remain. CHPA requests FDA to make the limit-setting process more transparent, e.g., provide visibility to NDSRIs that are under evaluation along with what information is needed to complete the review.

FDA: 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?

CHPA Comments:

Industry needs transparency and clarity on the limit setting process, specifically, what NDSRIs are being evaluated, what information is needed to support establishing a limit and what NDSRIs AIs have been approved without revealing the proprietary and confidential data used to establish those AIs. Access to existing data sharing forums (such as the Lhasa Complex Nitrosamines Consortium) requires membership fees and commitment to conduct studies, which is not feasible for many CHPA member companies. Additionally, without clarity on the study requirements (e.g., Ames study protocol designed to increase sensitivity for the detection of nitrosamines and as recommended by OECD (OECD 471, 1997, as corrected in 2020[3]), the studies conducted may need to be repeated.

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

FDA: 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?

CHPA Comments:

CHPA members have not received feedback to date from FDA regarding proposed AIs. Thus, it is currently unclear whether or not there will be challenges with meeting AI limits. As noted previously, several CHPA members have provided data and AI justification for NDSRIs well over a year ago and are still awaiting FDA feedback and lack clarity on what additional information FDA would require to support the proposed AI. This significant lag in feedback does not allow industry to comply with guidance timing for mitigation or even have the needed clarity as to the extent at which mitigation activities are even required. As such, CHPA requests FDA to extend and separate the timing for Step 2 and Step 3 as described above.

In addition to the feedback provided to the specific FDA questions/requests, CHPA members have the following requests:

- Dermal Exposure & Penetration:
  Industry proposes FDA issue guidance allowing for risk assessments to factor dermal penetration for larger molecular weight nitrosamines (e.g., > 500 daltons) into exposure assessments for dermally applied products.

- Need for FDA to Embrace Molar Correction for Higher Molecular Weight Nitrosamines: We highlight the pressing need for FDA and other regulatory bodies to embrace the concept of molar correction when addressing higher molecular weight nitrosamines, particularly in the context of NDSRIs (both API and impurity related). In the absence of an established AI specific to higher molecular weight nitrosamines, the current approach involves applying default AIs based on potent low-molecular nitrosamines (e.g., 26.5 ng/day). However, this approach lacks specificity and may result in overly conservative assessments for higher molecular weight NDSRIs. The concept of molar correction takes into account the molecular weight differences, allowing for a more accurate assessment of risk and appropriate establishment of impurity limits.

- Request for Clear Guidance on Bioequivalence Studies and Acceptance of Comparative Dissolution as a Surrogate:
  CHPA expresses concerns regarding the current uncertainty surrounding the FDA's expectations regarding bioequivalence studies in support of certain

manufacturing changes required to support nitrosamine mitigation. We request clear guidance outlining the FDA's expectations in this regard, specifically addressing the acceptance of comparative dissolution as a surrogate with defined acceptance criteria. The lack of explicit guidance on the required bioequivalence studies for such changes risk ambiguity and inconsistency in regulatory approaches.

CHPA members appreciate your thoughtful consideration of our recommendations and feedback. Please contact us if you have questions or need clarification.

Respectfully submitted on behalf of CHPA Members,

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[1] Ponting DJ, Foster RS, "Drawing a Line: Where Might the Cohort of Concern End?" *Organic Process Research & Development,* **2023**. https://doi.org/10.1021/acs.oprd.3c00008

[2] Trejo-Martin A., Bercu JP, Thresher A, Tennant RE, Thomas RF, Cross K, Czich A, Waese K, Nicolette JJ, Murray J, Sonders P, Kondratiuk A, Cheung JR, Thomas D, Lynch A, Harvey J, Glowienke S, Custer L, Escobar PA, "Use of the bacterial reverse mutation assay to predict carcinogenicity of N-nitrosamines" *Regulatory Toxicology and Pharmacology*, **2022**, vol 135. https://doi.org/10.1016/j.yrtph.2022.105247

[3] OECD (1997, as corrected in 2020), Bacterial Reverse Mutation Test, in OECD Guideline for the Testing of Chemicals, Test Guideline No. 471.