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Dockets Management
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 (Docket Number: FDA-2023-N-1585)

Dear Sir or Madam:

The Parenteral Drug Association (PDA) is submitting the attached responses on behalf of a group of our members regarding FDA's discussion paper on Identification, Assessment, and Control of Nitrosamine Drug Substance-Related Impurities in Human Drug Products. The paper provided the industry with FDA perspectives on this issue and PDA's members have collaborated to collectively reply to the questions posed by the agency. In the attached comments, the team offers insight and suggestions that may assist the agency in formalizing and finalizing guidance related to NDSRIs.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. These comments have been prepared by a group of volunteers with expertise in pharmaceutical and biopharmaceutical manufacturing with the aim of aligning on best practices and policies to ensure patient safety and continuity of drug supply.

If you have any questions, please do not hesitate to contact me via email at wright@pda.org.

Sincerely,

Glenn E. Wright
President and CEO

cc: Josh Eaton, PDA

Responses to "Issues for Consideration and Request for Comments"

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?

All the pertinent topics are discussed in the guidance; however, guidance from the FDA specific to what testing should be conducted to address the carcinogenicity risk and AI limits for NDSRIs would be appreciated.

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

The principles for conducting read-across assessments are clear, however the data set is extremely limited for appropriate molecules thus making these endpoints unreliable in some cases.
Currently, the selected read-across compounds selected may vary between Regulators and Sponsors. A defined framework for selecting read-across compounds could be provided so the same read-across compound would be selected by independent researchers. Also, providing clear criteria defining "sufficiently robust carcinogenicity data" such that compounds with robust carcinogenicity data (but with no Health Authority established control limits) could be used to derive NDSRI specific control limits would be ideal. Guidance or a final decision upon an acceptable enhanced Ames Test protocol would also benefit the industry so that if an NDSRI tests negative, there will be no need to follow up with an in vivo study (in line with ICH M7). Additionally, this group requests that the agency consider acceptance of other in vivo assays, such as duplex sequencing and comet assays.

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

The example of using drug product pH as a mechanistic principle to discharge the risk of NDSRI formation is good and should be considered in the mitigation control strategy. In addition, the use of formulation additives (functional excipients such as nitrosation inhibitors or scavengers) to inhibit the formation of NIs warrants further support. However, this may not be practical for marketed products.

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, follow up in vitro mutagenicity, in vivo transgenic gene mutation test) in support of establishing AI limits?

i. Acceptance of AMES results for negative outcomes on nitrosamines from the test. Clear guidance that recommends what needs to be done so Ames is fully acceptable would be a tremendous help (time, cost, resources, speed, and reliability) to the industry in managing nitrosamines.
ii. Consideration regarding both sensitivity and specificity when defining conditions for Optimized Ames Methodology. A methodology with too high a false positive rate would trigger more in vivo follow-up testing, wasting animals and saturating TGR (Transgenic Rodent) testing capacity.The same criteria could be provided for other in vivo assays.
iii. The minimum or recommended tissues required for a negative in vivo mutation test to be considered acceptable in support of a negative NDSRI risk.
iv. For NDSRIs that test positive in the in vivo assay, a recommended method for deriving mutagenic/carcinogenic potency (~50% of NDSRIs are showing positive results for both in vivo and in vitro assays).

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

i. Limited data has suggested that the in vivo Comet assay may be useful to detect DNA repair following nitrosamine DNA damage. However, insufficient data currently exists to confirm this observation. Guidance on acceptability of the use of NDSRI Comet data, in addition to Comet data from a read-across nitrosamine with carcinogenicity data would be helpful when selecting assays to include in a WOE data set for NDSRI hazard identification.

ii. Guidance on how to use existing mammalian in vitro assays (e.g., mouse lymphoma, HPRT) in a WOE assessment for NDSRI hazard assessment would be helpful. Guidance on how metabolism data can be used to support WOE would also be helpful (i.e., What does a sufficient WOE data set look like?).

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

In addition to the above comments, the 6-month mouse transgenic study is impractical for pharmaceutical companies due to availability of transgenic animals, study sites, cost, and duration.

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

Yes, see above comments.

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)?

Yes, see above comments.

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?

While the Agency has accommodated industry needs on NDSRIs related to interim AIs, the effort to get to a place of acceptance is significant. It will be good to include FDA's position and recommendation on interim AI as to how novel NDSRIs can be handled while the AI is being determined. This will help avoid drug shortage.

Additional time would be beneficial, knowing the limited availability to conduct these studies and the long duration to complete these assessments.

Clearer expectations on which studies should be conducted to develop NDSRI data and implement recommended AI limits for NDSRI based impurities would also be beneficial.

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?

Collaboration is already in progress in the form of data-sharing initiatives with current manufacturers (LHASA Data Sharing Initiative, HESI, and MutaMind). However, further guidance from the agency would be helpful on defining the type of compound-specific data of interest (e.g., in vivo, SAR data).

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?

Data sharing amongst competing companies is challenging. In order to be feasible, this must be conducted under the umbrella of trade associations with an honest broker as a mediator.

Additionally, it seems data sharing between regulatory agencies is also problematic. Proposed solutions have been made and the industry looks forward to this being resolved amongst the health authorities.

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?
There have been occasional instances of recalls, however most companies have been able to avoid this scenario for the sake of patient safety and availability of medicine.