EXHIBIT 17

Case 1:22-md-03050-KPF Document 44-17 Filed 06/20/23 Page 2 of 5

Updates on possible mitigation strategies to reduce the risk of nitrosamine drug substance-related impurities in drug products

FDA issued a guidance for industry, *Control of Nitrosamine Impurities in Human Drugs (/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs)*, in September 2020 to help ensure the safety of the U.S. drug supply by recommending steps manufacturers of active pharmaceutical ingredients (API) and drug products should take to detect and prevent objectionable levels of nitrosamine impurities in pharmaceutical products. The guidance also described conditions that may introduce nitrosamine impurities and described a three-step mitigation strategy.

The agency updated the guidance in February 2021 to specify timeframes for completion of nitrosamine mitigation activities by drug manufacturers. The strategy includes risk assessment (step 1), confirmatory testing if risks are identified (step 2), and reporting 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) (step 3).

FDA expects risk assessments (step 1) to have been already completed as the recommended completion date was March 31, 2021. FDA's recommended timeline for completion of confirmatory testing and reporting changes (steps 2 and 3) is October 1, 2023. With the risk assessment stage completed and approximately two years left for manufacturers to implement changes, FDA is providing manufacturers with additional points to consider in developing nitrosamine mitigation strategies, including consideration of the role of formulation design for controlling nitrosamine levels in drug products.

Recently, FDA has received additional reports of certain types of nitrosamine impurities that formed in several drug products. These nitrosamine drug substance-related impurities (NDSRIs) are a class of nitrosamines sharing structural similarity to the API. NDSRIs can be generated during manufacturing or during the shelf-life storage period of the drug product. In some cases, the root cause of NDSRI formation has been attributed to nitrite impurities present in excipients at parts-per-million amounts.[1] 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.

FDA expects manufacturers to ascertain the presence of nitrosamines, including NDSRIs, using the three-step mitigation strategy described in the agency's guidance. As manufacturers should now be engaged in the confirmatory testing and reporting changes stages of their

mitigation activities (steps 2 and 3), if NDSRIs are detected in the drug product at objectionable levels, FDA encourages applicants to develop control strategies and/or design approaches to reduce NDSRIs to acceptable levels.

One mitigation strategy described in FDA's guidance includes a supplier qualification program that takes into account potential nitrite impurities across excipient suppliers and excipient lots to reduce the risk of nitrosamine formation in the drug product. However, FDA recognizes that this is only one strategy, and other approaches may be equally or more effective in controlling nitrosamine levels. Therefore, FDA encourages manufacturers to explore other approaches to mitigate or prevent formation of NDSRIs. Examples of possible mitigation strategies related to formulation design are described below.

The first of these possible mitigation strategies is derived from literature reports showing that commonly used antioxidants such as ascorbic acid (vitamin C) or alpha-tocopherol (vitamin E) inhibit the formation of nitrosamines in vivo based upon data from human gastric fluid in vitro studies.[2,3] Recent work has employed this concept in formulation design and has preliminarily demonstrated that the addition of antioxidants to formulations may significantly inhibit the formation of NDSRIs in drug products.[4] A second possible approach is based upon 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.[2] Thus, formulation designs that incorporate excipients such as sodium carbonate that modify the micro-environment to neutral or basic pH, should in principle inhibit the formation of NDSRIs. Each manufacturer should determine the potential benefit from and demonstrate the suitability of any reformulation approach.

FDA encourages manufacturers to consider these as well as other innovative strategies to reduce the formation of NDSRIs to acceptable levels in drug products. FDA will consider meeting requests, as appropriate, to discuss innovative mitigation strategies with prospective applicants or manufacturers. Applicants may also choose to submit formulation changes through supplements or amendments to their applications without scheduling a meeting with FDA, and any manufacturer, including non-application drug manufacturers, may implement any formulation changes in accordance with appropriate current good manufacturing practice regulations and related guidance. We recommend that applicants or manufacturers interested in meeting with FDA prepare a comprehensive meeting package with the appropriate regulatory and scientific data using the above or other novel approaches to reduce the risk of nitrosamine impurities in drug products in accordance with existing guidance. We recommend the meeting request/package be submitted to the application as follows:

For NDA/BLA:

- Follow the draft guidance for industry Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (/regulatory-information/search-fda-guidance-

documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry).

For ANDAs

- Submit a meeting package as a general correspondence indicating "Meeting Request: Nitrosamine Mitigation Strategies". The meeting package should include
  - Brief statement of the purpose and objectives of the meeting
  - List of all individuals, with their titles and affiliations, who will attend the meeting from the prospective applicant's organization
  - Suggested dates and times of the meeting. The Agency will schedule the meeting based on availability of both FDA and applicant's availability
  - Proposed format of the meetings (i.e., written response, teleconference, or face-to-face)
  - Proposed agenda
  - List of questions for discussion
  - Data to support the discussion

The data in the NDA/BLA and ANDA meeting package should include, at a minimum, the following:

- Description of the formulation design strategy employed to reduce the formation of NDSRIs in the drug product.
- Supporting manufacturing information and, at a minimum, three months of accelerated stability data demonstrating control of NDSRI.
- For approved NDAs and ANDAs that require reformulation as part of a mitigation strategy, in vitro or in vivo bioequivalence bridging studies.

---

[1] Wu Y., et al. Reactive Impurities in Excipients: Profiling, Identification and Mitigation of Drug-Excipient Incompatibility, AAPS PharmSciTech, 2011, 12(4), p. 1248-1263

[2] Ziebarth, D. and Scheunig, G. (1976), Effects of Some Inhibitors on the Nitrosation of Drugs in Human Gastric Juice, Lyon International Agency for Research on Cancer International (IARC Scientific Publications 14) p. 279-290.

[3] Mergens, W.J. (1982) Efficacy of Vitamin E to Prevent Nitrosamine Formation, New York Academy of Sciences, Vol.393 (1), p.61-69.

Case 1:22-md-03050-KPF Document 44-17 Filed 06/20/23 Page 5 of 5

[4] Nanda, K. et al. Inhibition of N-Nitrosamine Formation in Drug Product: A Model Study, Journal of Pharmaceutical Sciences 2021 (August) on-line.