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December 20, 2024

Submitted via www.regulations.gov

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

Re: Control of Nitrosamine Impurities in Human Drugs. Guidance for Industry. September 2024. Docket No. FDA-2020-D-1530.

Dear Sir or Madam:

The Consumer Healthcare Products Association[1] ("CHPA") submits these comments in response to the U.S. Food and Drug Administration's ("FDA's" or the "Agency's") guidance for industry, Control of Nitrosamine Impurities in Human Drugs. For more than 143 years, CHPA has served as a vital advocate for the consumer healthcare products industry. A member-based trade association, CHPA represents the leading manufacturers and marketers of OTC medical products. CHPA members provide millions of Americans with safe, effective, and affordable therapies to treat and prevent many common ailments and diseases.

CHPA members appreciate the Agency releasing the revised guidance which provides recommendations for steps manufacturers of active pharmaceutical ingredients (APIs) and drug products should take to detect and prevent unacceptable levels of nitrosamine impurities in pharmaceutical products.

CHPA members have been working diligently on assessing potential for nitrosamine formation from APIs used in OTC medicines. Since this issue first surfaced, much has been learned and continues to be learned about nitrosamine impurities. Scientific understanding and related research will continue to evolve. Scientific dialogue with FDA and sharing of information have been generally slow to happen until recently and we are hopeful FDA will create more opportunities to interact and to share scientific data and best practices going forward. We encourage FDA to use its website for timely updates.

[1] The Consumer Healthcare Products Association (CHPA), founded in 1881, is the national trade association representing the leading manufacturers and marketers of consumer healthcare products, including over-the-counter (OTC) medicines, dietary supplements, and consumer medical devices. CHPA is committed to empowering self-care by ensuring that Americans have access to products they can count on to be reliable, affordable, and convenient, while also delivering new and better ways to get and stay healthy. Visit www.chpa.org.

[2] FDA: Control of Nitrosamine Impurities in Human Drugs; Guidance for Industry; Availability. Accessed from: https://www.govinfo.gov/content/pkg/FR-2024-09-05/pdf/2024-19883.pdf on December 20, 2024

Comments

Page 23 – FDA recommends conclusion of NDSRI confirmatory testing of drug products and submission of required changes in drug applications by August 1, 2025. This timeline was established in 2023 and for our industry, it is unrealistic. Evolution of understanding nitrosamine formation in finished products has been slow and while progress is being made, much remains to be done. This includes standardization of assays for nitrosamine impurities, generation of additional data and possible submission of alternative acceptable limits to FDA for review and approval. Until very recently, our members have been unable to get necessary feedback from FDA on research programs and other steps towards further understanding NDSRI safety. A more realistic timeline for our industry is August 2027 to complete all necessary work for full implementation, including Enhanced Ames Tests (EATs) and generating other potential safety data, reformulation, manufacturing validation and stability testing.

As an example of the challenges we are facing, one of the preferred routes of remediation is to replace high-nitrite excipients with low-nitrite materials, since this approach avoids extensive changes to the formulation. Our experience to date with excipient sourcing is that manufacturers are making slow progress on the provision of low-nitrite materials. Additionally, where these are available, the replacement of the excipient may not provide sufficient remediation alone and additional remediation steps may be required. This could, for example, include the addition of an antioxidant which needs to be carefully selected and optimized to minimize other effects on the formulation (e.g., could impact bioavailability, appearance, impurity profile, etc.). To demonstrate the effectiveness of any remediation step taken, testing is required, including generation of stability data.

FDA feedback on proposed limits or mitigations is expected to take at least a year based on prior experience. Taken together, these steps support our proposal of August 2027 as a realistic and rational implementation date.

Pages 11-13 – When considering acceptable intakes of nitrosamines, CHPA encourages FDA to continue to participate and consider insights from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the Health and Environmental Sciences Institute (HESI), including adopting Less-than-Lifetime (LTL) exposure limits for products with appropriate justification. We feel this is particularly appropriate for OTC medicines, many of which are used on an acute basis. It would also accord with policies currently in place elsewhere in the world. We appreciate FDA's interactions with global regulatory authorities and ask that FDA consider approaches, such as in Europe, where a 30% threshold for reduced (e.g., skip) testing is acceptable for nitrosamines.

We appreciate FDA's consideration of these comments and look forward to ongoing sharing of new insights about nitrosamines and dialogue with FDA on matters related to specific OTC medicines and the respective APIs.

Respectfully submitted,

Frederick Meadows

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