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Whitepaper on

Human medicinal products containing nitrosamine impurities:

Regulatory landscape in the United States and the European Union

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Nitrosamines are common chemicals in water and foods including cured and grilled meats, dairy products, and vegetables. Nitrosamine impurities may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time. However, a person taking a drug that contains nitrosamines at, or below, the acceptable daily intake limits every day for 70 years is not expected to have an increased risk of cancer. Different regulatory bodies (including Food and Drug Administration [US FDA] and European Medicines Agency [EMA]) are investigating the presence of nitrosamine impurities in some types of medications.

The FDA, in collaboration with regulatory counterparts around the world, has set internationally recognized acceptable daily intake limits for nitrosamines. If drugs contain levels of nitrosamines above the acceptable daily intake limits, the FDA recommends that these drugs be recalled by the manufacturer as appropriate.

Manufacturers are responsible for understanding their processes, which includes preventing the presence of unacceptable impurities. Manufacturers are also responsible for developing and using suitable methods to detect and limit unacceptable impurities, including any new impurities that may arise when they make changes to their manufacturing processes.

A comparison of US FDA and EMA regulatory expectations in this regard is given below:

EMA Nitrosamine Impurities Guidance	USFDA Nitrosamine Impurities Guidance
• EMA/369136/2020 • Assessment report[1] • Procedure under Article 5(3) of Regulation EC (No) 726/2004 • Nitrosamine impurities in human medicinal products[2]	• Control of nitrosamine impurities in human drugs • Guidance for industry[4] • This guidance is for immediate implementation
Applicable for	
• drug products containing chemically synthesized drug substance, • chemically synthesized drug substance • biological medicinal product • For marketed products, under approval applications and applications to be submitted	• drug products containing chemically synthesized drug substance • chemically synthesized drug substance • For marketed products, under approval applications and applications to be submitted
Publishing Date	
• On 19/Sep/2019 • Revised on 25/Jun/2020	• On 01/Sep/2020
Notification to agency	
The risk assessment outcome needs to be submitted to the EMA/ National competent authorities (depending upon filing procedure) as per templates available on the EMA website[3]. (Templates available for : Step-1: No risk identified template Step-1: Risk identified response template Step-2: No nitrosamine detected template Step-2: Nitrosamine detected template	• If no risk is identified, no further action is required. Nitrosamine risk assessment report should be available if requested. • If risk is identified, confirmatory testing to be done as soon as possible and application to be amended.
Timeline: • Step-1: No risk identified • Step-2: Confirmatory testing • Step-3: Variation is concluded for corrective steps to control nitrosamine impurities in approved applications **Step-1: No risk identified** For Biological medicines – 01/Jul/2021 For Chemical medicine – 31/Mar/2021 **Step-2: Confirmatory testing** Perform testing on the Nitrosamine risk identified products and report confirmed presence of nitrosamines as soon as possible **Step-3: Update marketing authorisation** For Chemical Medicines – 26/Sep/2022 For Biological Medicines – 01/Jul/2023	**Timeline:** • Risk identification to be done by 28/Feb/2021 for all marketed product • If risk identified, application needs to be amended/prior approval supplement/changes to the approved submissions to be submitted and concluded by 31/Aug/2023.

APCER has an expert team of Chemistry Manufacturing and Controls (CMC) reviewers who can support their clients in risk identification, impact assessment, and preparing a mitigation plan to cater the above-stated expectations.

References

1. Available from: https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf. . accessed online on October 30, 2020.
2. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/article-53-opinions#nitrosamine-impurities-in-human-medicinal-products-containing-chemically-synthesised-active-pharmaceutical-ingredients-(updated-18-october-2019)-section accessed online on October 30, 2020
3. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities#guidance-for-marketing-authorisation-holders-section. accessed online on October 30, 2020
4. Available from: https://www.fda.gov/media/141720/download. accessed online on October 30, 2020

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