General Chapter Prospectus: <1469> Nitrosamine Impurities

Posting Date: 24–Apr–2020
Expert Committee: General Chapters—Chemical Analysis
Input Deadline: 22–May–2020
Proposed New Title: <1469> Nitrosamine Impurities.

Suggested audience: Suppliers and manufactures of drug substance, drug products, excipients, contract manufacturing organizations, drug testing organizations and drug products related regulatory agencies, QA/QC specialists

Estimated proposal PF: *Pharmacopeial Forum* 46(5) [Sep.–Oct. 2020]

Background and objective(s): USP intends to develop a new informational general chapter to align with current scientific and regulatory approaches to provide information useful for ensuring the appropriate control of nitrosamine impurities in drug substances and drug products.

Description of scope and application: To provide a risk-based approach for the control of nitrosamine impurities in order to reduce or eliminate their presence in drug products. The chapter provides suitable performance criteria for analytical procedures used in the Identification and quantification of nitrosamine impurities.

Preliminary outline: The following represents the sections for the proposed General Chapter

- INTRODUCTION
- SOURCES OF NITROSAMINES-The sources by which the nitrosamines could be introduced in pharmaceutical products include, but are not limited to: a) API and/or raw materials processing under certain conditions; b) presence as impurities in raw materials, recycled solvents, reagents or catalysts; c) synthetic pathways; d) as impurities in some packaging systems; etc.
- NITROSAMINE RISK ASSESSMENT- DEVELOPMENT OF A CONTROL STRATEGY- A flow chart for a control strategy which also incorporates inputs from a cause and effect Ishikawa diagram evaluation of materials and processes in the production of drug substance

and/or drug products for the likelihood of nitrosamine presence.

- LIMITS OF NITROSAMINES-The section provides information on how to derive drug product concentration limits based on the acceptable daily intakes established by regulatory agencies.
- TEST PERFORMANCE CHARACTERISTICS OF NITROSAMINE PROCEDURES – This section provides recommended acceptance criteria for analytical procedures performance to be used in detecting and quantifying nitrosamines
- IDENTIFICATION, CONTROL, AND QUANTIFICATION OF NITROSAMINES-Several analytical procedures are included in this section with the information on the specific nitrosamine(s) they are applicable for and the specific official articles for which they have been validated or verified. The section includes considerations for sample preparations based on the experience of USP Laboratories and drug manufacturers collaborating with USP

Anticipated implementation timing: To be determined based on stakeholder feedback.

Additional Information: USP has developed a comprehensive portfolio of USP Reference Standards for nitrosamine impurities including, N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA), N-Nitrosodiisopropylamine (NDIPA), N-Nitrosodibutylamine (NDBA), N-Nitrosoethylisopropylamine (NEIPA), and N-Nitrosomethylaminobutyric Acid (NMBA). The new reference standards are expected to be available in late spring 2020.

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