Part 2

NITROSAMINE

Presented by cGALP

Root cause for the presence of Nitrosamine in Drug Substance and Drug Product

Root cause for the presence of Nitrosamine in Drug Substance

❖Nitrosamine formation – General condition

- Formation of Nitrosamine impurity in presence of secondary, tertiary, or quaternary amines and nitrite salts under acidic reaction conditions
- Nitrite salts may form nitrous acid which can react with an amine to form a nitrosamine
- Greater risk of nitrosamine formation if nitrous acid is used to quench residual azide in the presence of precursor amines
- Use of nitrites in the presence of secondary, tertiary, or quaternary amines are at risk of generating nitrosamine impurities.

Root cause for the presence of Nitrosamine in Drug Substance

❖**Nitrosamine formation – Sources of amines**

- Sources of Secondary, Tertiary and Quaternary Amines That Can Form Nitrosamines
- Amines(Secondary and Tertiary) present in the manufacturing process in API, intermediate and starting materials
- Tertiary and quaternary amines may also be added intentionally as reagents or catalysts
- Amide solvent is another source of amine. Amide will degrade certain condition and form amine
- N,N-dimethylformamide can degrade into dimethylamine.
- N-methylpyrrolidone, N,N-dimethylacetamide, and N,N-diethylacetamide also have similar degradation pathways to form secondary amines
- All the amine can react with nitrous acid to form nitrosamine impurities
- Other reagents containing amine functional groups for potential risk of nitrosamine formation.

Root cause for the presence of Nitrosamine in Drug Substance

❖ ***Contamination in Vendor-Sourced Raw Materials***

- Nitrosamine contamination - when fresh solvents (*ortho*-xylene, toluene, and methylene chloride) were contaminated during shipment from vendors (e.g., during transfer between storage vessels).
- Sodium nitrite is a known impurity in some starting materials (such as sodium azide) and may be present and react with amines under acidic conditions to form nitrosamines.
- Nitrate-containing raw materials, such as potassium nitrate, may contain nitrite impurities.
- Secondary or tertiary amines have been reported as impurities in some raw materials and in fresh solvents such as toluene.
- Starting materials or outsourced intermediates may be at risk through cross-contamination if they are manufactured at sites where nitrosamine impurities are produced in other processes.

Root cause for the presence of Nitrosamine in Drug Substance

❖Recovered Solvents, Catalysts, and Reagents as Sources of Contamination

- Recovered materials such as solvents, reagents, and catalysts may pose a risk of nitrosamine impurities due to the presence of residual amines (such as trimethylamine or diisopropylethylamine).
- If the recovery process involves a quenching step (i.e., nitrous acid used to decompose residual azide), nitrosamines could form during solvent recovery.
- use of recovered solvents that are coming from different processes or across manufacturing lines without control and monitoring can introduce nitrosamine impurities
- Recovery of raw materials (e.g., solvents, reagents, and catalysts) is often outsourced to third-party contractors. Process outsourcing can pose a risk if the third-party recovery facility does not receive enough specific information on the contents of the materials they are processing and relies solely on routine recovery processes.

Root cause for the presence of Nitrosamine in Drug Substance

❖Recovered Solvents, Catalysts, and Reagents as Sources of Contamination

- Raw materials can be contaminated if adequate cleaning of equipment between customers, or between different materials, is not carried out or is not validated as capable of removing each impurity of concern.
  - *ortho*-xylene and toluene were contaminated during recovery due to inadequate cleaning and to use of shared storage equipment between different customers.
- Inadequate and unvalidated cleaning procedures can also lead to cross-contamination if precautions to avoid nitrosamine contamination are not in place before materials from different customers are combined for recovery.
  - For example, the catalyst tri-N-butyltin chloride (used as a source of tri-N-butyltin azide) was contaminated at a third-party contractor facility due to the combination of this catalyst from different customers.

Root cause for the presence of Nitrosamine in Drug Substance

- **Quenching Process as a Source of Nitrosamine Contamination**
  - There is a risk of nitrosamine formation when a quenching step is performed directly in the main reaction mixture (i.e., when nitrous acid is added to the reaction mixture to decompose residual azide). This allows nitrous acid to come into direct contact with residual amines in the raw materials used in the manufacturing process.
  - The nitrosamine impurities could be carried to the subsequent steps if there are not adequate removal or purification operations in place, or if the operations are not optimized for removing specific impurities of concern.

Root cause for the presence of Nitrosamine in Drug Substance

❖Lack of Process Optimization and Control

- Another potential source of formation of nitrosamine impurities is lack of optimization of the manufacturing process for APIs when reaction conditions such as temperature, pH, or the sequence of adding reagents, intermediates, or solvents are inappropriate or poorly controlled.

Nitrosamine Impurities in Drug Products From Sources Other Than API Contamination

- Nitrites are common nitrosating impurities that have been reported in many excipients at ppm levels.
- Nitrite impurities are found in a range of commonly used excipients, which may lead to nitrosamine impurities forming in drug products during the drug product manufacturing process and shelf-life storage period.
- Nitrosamine impurities may be present in potable water
- Some drug products may undergo degradation pathways that form nitrosamine impurities; this could potentially occur during drug product storage.