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Developing Processes for Nitrite-Free Excipients

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FDA Guidance – Nitrosamine Impurities

- Per ICH M7 Nitrosamines are in the "cohort of concern". They are mutagenic carcinogens in animals and possibly in humans.
- FDA's February 2021 Guidance for Industry, *Control of Nitrosamine Impurities in Human Drugs*, requires nitrosamine risk assessments (RA) and mitigation of risks.
- The guidance lists seven (7) common nitrosamine impurities and recommends acceptable limits for six (6). FDA and USP have also published analytical methods for these common nitrosamines.
- FDA acknowledges that there are other nitrosamines which can be formed based on the API manufacturing process or structure and recommends that these be controlled at 26.5 ng/day.
- Nitrites have been identified as the major source of nitrosamine risk as they are common in many excipients and are instrumental in nitrosamine formation.

Source of Nitrosamines in Pharmaceuticals

- Nitrosamines are formed when secondary and tertiary amines react with nitrites or other nitrosating agents.
- While quaternary amines are generally not known to nitrosate easily, they may have secondary and tertiary amines as impurities which can then form nitrosamines.
- Any source of nitrite (or nitrate which can reduce to nitrite) can increase the risk of nitrosamines in formulations.
- Drug product formulations consist of one or more APIs and excipients
  - APIs are manufactured under cGMP conditions
  - Excipients, which may be the major constituents of a formulation, are predominantly manufactured under non-cGMP conditions
  - Pharmaceutical industry demand for excipients constitutes only a small fraction of the market for excipient manufacturers which makes it difficult for them to meet the nitrosamine requirements

Nitrosamine Risk from Excipients

- Several excipients are known to have residual nitrites and nitrates (Wu, et al. AAPS PharmSciTech, 2011, 12(4), 1248-1263)
  - Examples: Microcrystalline Cellulose, Pregelatinized Starch, Sodium Starch Glycolate, Povidone
- Controlling nitrites and nitrates in excipients is challenging
  - Detecting and quantitating at “ppb” levels in the formulation matrix is difficult (interference from the soluble and insoluble components)
  - The global nature of excipient manufacturing makes it difficult to understand excipient quality
- APIs which are themselves secondary amines may form the corresponding nitrosamines during manufacturing and storage due to reaction with nitrites in excipients
- Amine impurities in APIs may aslo react with nitrites originating from excipients
- Excipient- excipient interactions
  - In rare instances, excipients may have amine residues which could react with the nitrite residues in other excipients in the formulation to form nitrosamines

Impact Risk from Nitrites in Excipients

As excipients generally constitute the major portion of a drug formulation, not addressing the risk of nitrosamines arising from nitrites in excipients may:

- Make it difficult to remediate the risk when the API is a secondary amine, or when there are impurities in the API or the excipients which are themselves secondary amines
- Necessitate reformulation of drug products and/or the conduct of expensive *in vivo* studies to justify nitrosamine limits
- Result in the withdrawal of drug applications
- Deter or impede development of critical, much needed medications
- Delay market introduction of affordable generic drugs
- Result in drug shortages

All of the above may impact the availability of cheaper generic drugs to the American Public

Remediation

We can remediate the risk of nitrosamines by:

- Controlling the nitrite level in excipients, preferably at “ppb” level, to reduce the risk of nitrosamine impurities in drug products
  - Testing for nitrites in drug product formulations is complicated by the complexity of the matrix and solubility or lack of solubility of excipients which may interfere with the analysis

- Identifying the root cause of nitrites in excipients, and/or developing commercial processes for manufacturing nitrite-free excipients
  - Excipient manufacturers may not have the necessary resources to develop processes
  - There is undue burden on drug product manufacturers to evaluate the presence of nitrites in every lot of excipient

How can FDA Help?

FDA can support a collaborative effort to understand the source of nitrites in excipients and propose improvements in the manufacturing process of excipients leading to desirable nitrite levels

Thank you