IPEC Position Paper

The Role of Excipients in Determining N-Nitrosamine Risks for Drug Products

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Purpose of Position Paper

This paper describes the IPEC Federation's (IPEC) position on the role of excipients when conducting N-nitrosamine (nitrosamine) risk assessments for drug products.

Executive Summary

The presence of N-nitrosamines in drug products continues to be a global concern. Contributions excipients may or may not have on nitrosamine formation should be considered within a holistic risk assessment for drug products. Although the risk for excipients to directly contribute nitrosamines to a drug product is very low, some excipients may contain the reactive species that contribute to (or inhibit) nitrosamine formation. The most likely reactive species potentially present in excipients are nitrosating agents, like nitrites. The concentration of nitrites may differ by excipient chemistry, manufacturer and batch. Excipient manufacturers, on their own, have no regulatory requirement to conduct risk assessments or control reactive species within their products. The responsibility of assessing and potentially controlling nitrosamines lies with the drug product owner/manufacturer as part of a collaborative process. However, many excipient manufacturers provide information to support drug product manufacturers' risk assessments and mitigation strategies (IPEC-Federation Questionnaire).

Background Information

N-nitrosamines are a class of organic compounds that include examples that are associated with a potential for a significant carcinogenic risk (part of the "cohort of concern" in ICH M7).[1] Beginning in July 2018, the European Medicines Agency (EMA) reported the recall of several products containing Valsartan due to *N*-nitrosodimethylamine (NDMA) contamination.[2] This initiated investigations by several regulatory agencies resulting in the discovery of N-nitrosamine impurities in sartans and other unrelated compounds.[3,4] Because the presence of N-nitrosamines in final drug products is a global issue, there have been requests from multiple regulatory agencies for drug product manufacturers to complete risk assessments for the presence or formation of N-nitrosamines in marketed drug products containing chemically-synthesized APIs.[5] In July 2020, the EMA published an Article 5(3) assessment report that placed all medicinal products (including, biologics, vaccines, Advanced Therapeutic Medicinal Products (ATMPs), and recombinant therapeutic proteins) into scope of the nitrosamine risk assessment.[6,7] Other regulatory agencies, (for example, Health Canada, Swiss Medic, and ANVISA) have also placed biologics within scope of the nitrosamine risk assessments. In September 2020, the US Food and Drug Administration (FDA) published its guidance on nitrosamines.[8] The FDA's guidance applies to any drug product containing chemically synthesized APIs and drug products at risk.

The most substantial risk for the presence or formation of N-nitrosamines in drug products comes from the confluence of three factors: a nitrosating agent, a secondary or tertiary amine (vulnerable amines),

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and appropriate conditions (for example elevated temperatures, acidic conditions, liquid phase) for the reaction. This position paper does not intend to be an exhaustive review of nitrosamine chemistry and formation. For further details on nitrosamine formation, please refer to published articles.

Excipients should be considered within a holistic risk assessment for nitrosamines in a drug product. Risk assessments by the drug product manufacturer should be designed to evaluate the potential sources of nitrosamine presence/formation (i.e., API including starting materials, route of synthesis, solvents, solvents recovery, degradation of API, excipients, primary packaging material) and contamination during manufacturing of drug products.

IPEC Federation Position

Nitrosamines in Excipients

To date, only one excipient has been known to contain a nitrosamine: trolamine (triethanolamine) with the nitrosamine impurity N-nitrosodiethanolamine. In the European Pharmacopeia, the limit for N-nitrosodiethanolamine is established at 24 ppb.[9] While this particular excipient may contain a nitrosamine impurity, this vulnerability is known and understood. The risk of an excipient introducing a nitrosamine directly to a drug product is not currently envisaged for any other product.

Vulnerable Amine Compounds in Excipients

Vulnerable amines can be introduced to a drug product via the active drug substance, impurities in the active drug substance, counterions from pharmaceutical salts, and excipients. With respect to excipients, the questions that should be considered are: can an excipient directly introduce a reactive amine that can convert to a nitrosamine within a drug product? The potential risk that may come from a vulnerable amine present in trace amounts in an excipient will depend on the formulation composition and should be evaluated accordingly.

Nitrosating Compounds in Excipients

Concern for nitrosating compounds in excipients has focused attention on nitrites and nitrates, neither of which are powerful nitrosating compounds on their own, but, under certain conditions, can potentially react with other materials in the drug product formulation to form nitrosamines. Nitrite can form the reactive species nitrous anhydride (N_2O_3) under mildly acidic conditions.[10] Solid state mechanism of nitrosamine formation related to nitrite partitioning in water vapor and reacting with secondary amine containing APIs have been reported.[11] Nitrates can react to form nitrite through enzymatic reduction, which then can form the reactive nitrous anhydride under acidic conditions.[12] It is very unlikely during excipient and drug product manufacturing for enzymatic reduction of nitrates to nitrites to occur. Therefore, nitrate is not a significant contributor to nitrosamine formation in drug products.[13,14,15] Further discussion will focus only on nitrites.

The report by Wu et al. measured nitrites in samples of microcrystalline cellulose (MCC), lactose, pre-gelatinised starch, povidone, crospovidone, sodium starch glycolate (SSG), sodium croscarmellose, stearic acid, hydroxypropyl cellulose (HPC) and silicon dioxide.[16] Reported levels of nitrites in the excipients ranged from 0.9 ppm (in a sample of HPC) up to 285.6 ppm (in a sample of SSG). More recently, a publication from Lhasa provides ranges of nitrites in excipients as reported by contributor companies.[14] The report indicates that nitrite levels can vary batch-to-batch and manufacturer-to-

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manufacturer and are dependent on the method used to quantify nitrites. These reports highlight the complexity that arises when assessing the potential contributions of nitrosating agents from excipients.

It is important to note that the presence of nitrites cannot always be directly inferred from the structure or manufacturing process. Process water (e.g., material used for washing materials after processing), raw materials, and excipient processing conditions could be sources of nitrites in excipients. Excipient manufacturing can use potable and/or purified water. Typically, potable water has nitrite levels below 0.1 ppm and would not likely be a concern as a source of nitrosating agents.[10] Where purified water is used to manufacture excipients, it is even less likely a factor of concern. Typically, purified water and potable water undergoes periodic testing and reporting of control levels for numerous chemical moieties including monitoring and controls for nitrites. It is important to know that the water used for washing the material, for instance after acid mediated processes, can be extensive and that some materials can preferentially adsorb content from the water, so processing water needs to be of the requisite standard (at a minimum, potable water).

While nitrites are present in commonly used excipients, removing nitrites from excipients, where present, is not trivial. Rather than removing or limiting nitrites in excipients, the impact of nitrites in a given excipient should be evaluated individually for each drug product for any potential risk. Whether the presence of nitrites in an excipient is a significant risk factor will depend on the composition in the drug product formulation and the published acceptable level for a given nitrosamine. It is possible that, going forward, that alternate sources of water could be used for processing excipients, but this will have an impact on how much it costs to process them with more expensive sources of water.

So, is it necessary to introduce limits for nitrites in excipients? For each drug product, the drug manufacturer must develop control strategies based on their risk assessment, for the following reasons:

- The presence of nitrites in an excipient alone does not directly result in the formation of nitrosamines in a drug product, as other factors (a vulnerable amine and correct reaction conditions) are also required. Not all drug products meet all conditions for nitrosamine formation.
- The amount of nitrite present in a drug product because of an excipient is dependent upon the amount of excipient used in the formulation.
- Mitigation in the form of exclusions of moisture, and conditions of oxidation, from the drug product by formulation, processing and packaging may be possible.

However, a thorough risk assessment on the drug product by the MAH or drug product manufacturer may conclude that the presence of nitrites in an excipient is a risk for nitrosamine formation. In such cases where possible, the MAH or drug product manufacturer should mitigate any risk in cooperation with the excipient supplier(s). Here, a limit for nitrites may be appropriate. However, it may not be possible for the vendor to meet any specific limit request, and the drug manufacturer needs to take this into account when making the risk assessment. For new products it is possible that grades, or suppliers, of materials may be chosen which act as a mitigation, but it may not be possible to retrofit these standards to long established materials.

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Consideration of Excipients for Mitigating Nitrosamine Formation in Drug Products

There are many opportunities for drug product manufacturers to select and utilize excipients to help reduce nitrosamine formation. Ideally this is best done as part of new product development (Quality by Design). Many new and novel nitrosamines are emerging and the scope of potential nitrosamines in commercial drug products is not yet fully understood. In 2021, the FDA provided updates on possible strategies to reduce the risk of nitrosamine impurities in drug products.[8] Within the update, the FDA encourages drug product manufacturers to explore innovative strategies to reduce the formation of nitrosamines in drug products. This is aligned with the investigation presented by Nanda where excipients (e.g., antioxidants and amino acids) were used to prevent the formation of nitrosamines within tablet formulations.[17] Additionally, certain amino acid and primary amine excipients have been shown not to be carcinogenic and/or to have scavenging and other nitrosamine inhibition formation properties.[18-23]

Responsibilities of Excipient Users

As communicated by regulatory agencies, the drug product manufacturer and/or MAH are responsible for completing a comprehensive risk assessment for the final drug product and sharing that as directed with the appropriate regulatory authorities. Care should be given when excipients are evaluated as an input for the drug product nitrosamine risk assessment to ensure proper conclusions are made. Considerations for the potential sources and processes that may contribute to the formation or contamination of nitrosamines should be thoughtfully evaluated. While excipients are typically not considered a major risk factor in terms of themselves being a direct source of nitrosamines, it is important to understand residual levels, if any, of nitrites that may be present in an excipient and that can potentially interact with other materials such as an API and/or API fragments. For these specific cases, the reader should refer to nitrosamine drug substance-related impurities (NDSRI) guidance per regulatory bodies like FDA, Health Canada and EMA. Collaborative discussions between the excipient manufacturer and the drug product manufacturer, drug product distributor, and/or MAH should occur when needed to ensure available excipient information is understood within its proper context. The ultimate goal is to ensure safe and effective medications are available for the treatment of patient ailments.

Responsibilities of Excipient Suppliers

As the previous sections highlight, nitrosating agents and vulnerable amines may be found in some excipients, but the responsibility for overall risk assessment for the presence of nitrosamines in a drug product lies with the MAH or the drug product manufacturer. So, how should excipient manufacturers and/or suppliers support MAHs with global supply chains with their risk assessments? First, IPEC recommends use of the IPEC questionnaire because it is in the interests of excipient manufacturers to provide information that would facilitate the safe use of their excipients generally, and equally for nitrosamines risk assessments; however, it should be made clear that excipient manufacturers are under no specific regulatory requirement to provide excipient risk assessments on nitrosamines to regulatory agencies.

Available Information on Nitrosamines

Until the recent reports from regulatory authorities that nitrosamines were found in drug products, there was little cause for excipient manufacturers to contemplate the potential presence of nitrosamines or nitrosating agents in excipients. Therefore, excipient manufacturers typically do not

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have substantial databases of information on the nitrite content of their systems, and any products which formed nitrosamines in use. Such information may not have been shared by the drug manufacturer with the vendor. On the other hand, excipient manufacturers generally have a detailed understanding of the manufacturing processes and the basic chemistry of the raw materials used. It is often possible to rule out the potential presence of nitrites based on this understanding. So, in summary, excipient manufacturers may be able to provide information that would potentially exclude the presence of nitrosamines, nitrosating agents (nitrites), or vulnerable amines, but they generally will not possess analytical testing data on these substances.

Format for Providing Information to Excipient Customers/Users

IPEC has developed a questionnaire template that guide an excipient manufacturer through a series of questions to provide information about a given excipient and its manufacturing process to help inform the drug product manufacturers risk assessments. Many excipient manufacturers have been using this template or similar formats to inform drug product manufacturers. The template can be used as a starting point for providing excipient information to customers. The template is publicly available on the IPEC website (IPEC Federation Questionnaire).

Reasonable Expectations / Misperceptions

Most excipient manufacturers are willing to share insights into the manufacturing processes for their products to potentially rule out the likelihood for nitrosamines. The IPEC questionnaire templates are good resources for excipient manufacturers to provide information on this topic, and their use is encouraged.

Excipient manufacturers have fielded many requests for information on nitrosamines over the past couple of years and have seen a few misperceptions that should be addressed.

- Responsibility for drug product risk assessment – this lies solely with the MAH or the drug product manufacturer though excipient manufacturers are generally providing information to support such assessments. While the regulatory responsibility is with the MAH, the excipient supplier should carefully evaluate the potential risks of its excipient. A risk assessment for an excipient is not a regulatory requirement for excipient suppliers, but they may play a role in evaluating the risk.
- Obligation to test – some drug product manufacturers have indicated that an excipient manufacturer should test their excipients to confirm the absence of nitrosamines and nitrites or provide typical levels. Excipient manufacturers are under no obligation to test excipients for these substances. Excipient manufacturers could voluntarily provide such data in cases where it is deemed to be warranted.

It is important to note that the presence of nitrites in current or historic material is not a failure of "Quality," as this parameter is generally not included in any quality requirement in Certificates of Analysis or Pharmacopeia.

Path forward / Summary

IPEC continues to monitor regulatory developments related to nitrosamines and drug products and any impact these may have on excipients or excipient manufacturers. The presence of nitrogen-

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containing components in an excipient does not necessarily lead to the formation of nitrosamines in a drug product. To assist drug product manufacturers to fulfil their regulatory obligations in conducting risk assessments for their drug products, IPEC encourages excipient manufacturers to share relevant information using tools such as the IPEC questionnaire. Only the drug product manufacturer, drug product distributor, and/or MAH can determine the potential risk of nitrosamine formation in the context of the other components in specific formulations and manufacturing, packaging, and storage conditions.

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