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

The Issue

The presence of N-nitrosamines in drug products continues to be a global concern. Excipients are considered as a potential risk factor during the drug product risk assessment. The focus of this position paper is to expand on the potential contribution excipients may or may not have on the formation of nitrosamines in final drug products. The presence of nitrites and vulnerable amines in excipients are also considered.

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.[5,6] 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.[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 medicinal products comes from the confluence of three factors: a nitrosating agent, a secondary or tertiary amine, and appropriate conditions (for example elevated temperatures, acidic conditions, liquid phase) for the aforementioned to react.

Toxicology literature has shown a linkage between nitrosamines and carcinogens in laboratory animals.[9, 10] However, epidemiology studies have provided less evidence of a linkage between nitrosamines and carcinogens in humans.[11] Based on the (1) allowable daily consumption of nitrites/nitrates, (2) naturally occurring nitrosamine content in foods and reported levels of daily nitrosamine exposure in the diet, and (3) daily endogenous nitrosamine production, any exposure to

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nitrites and/or nitrates in an excipient would cause humans to be exposed to significantly lower levels of nitrites/nitrates than the current limits established for food consumption, and to lower levels of nitrosamines than those from the diet and produced endogenously.

Risk assessments by the drug product manufacturer should be designed to evaluate the potential sources of nitrosamine formation and contamination during manufacturing of drug products. The risk of the presence of nitrosamine compounds within excipients itself is very low; however, many excipients contain traces of nitrites that can result in formation of nitrosamines under specific conditions within the drug product. The IPEC questionnaires (IPEC-Americas Template, IPEC-Europe Template) identify checkpoints, namely the manufacturing process, vulnerable amines and nitrosating agent, to be assessed.

Excipient manufacturers are diverse. Some manufacturers are large multinational chemical companies whose sales to the pharmaceutical industry represent a small fraction of their overall sales. Other manufacturers are small but focused on highly regulated markets such as pharmaceuticals, dietary supplements, and food. Excipient manufactures may derive products from natural sources such as mines or botanical sources, and others may synthesize products from smaller chemical building blocks. Some excipient manufacturers may also produce simple mixtures of excipients obtained from other excipient manufacturers. In such cases, the excipient manufacturer is often in a similar situation to the Marketing Authorisation Holders (MAH) i.e., they are dependent on other excipient manufacturers to provide technical and regulatory information. And even those excipient manufacturers that synthesize products from smaller building blocks will outsource raw materials supplies, so are again dependent on those raw material suppliers for information, in many cases.

With such a broad range of excipient suppliers comes varied approaches to providing information on products and responding to customers regarding regulatory and technical questions. As a proactive approach, excipient manufacturers could include the relevant and available information on nitrosamine impurities for an excipient in the form of a declaration to customers to mitigate the risk in drug product development. IPEC questionnaires can provide the specific data to facilitate such evaluations. The risk due to the possible presence of nitrosating agents, vulnerable amines, or nitrosamines in excipients requires some perspective to provide the proper context for any perceived risk. The risk coming from an excipient will depend on the formulation components in the drug product, including the active pharmaceutical ingredient (API), and the amount of the excipient used in the formulation.

IPEC Federation Position

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 to form nitrosamines. Nitrite can form the reactive species nitrous anhydride (N_2O_3) under mildly acidic conditions.[12] Nitrates can react to form nitrite through enzymatic reduction, which then can form the reactive nitrous anhydride under acidic conditions.[13]

The report by Wu et al. measured nitrates and 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.[14] Reported levels of

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nitrites in the excipients ranged from 0.9 ppm (in a sample of HPC) up to 285.6 ppm (in a sample of SSG). Nitrate levels ranged from 3.5 ppm (HPC) to 183.1 ppm (SSG).

Water, raw materials, and excipient processing conditions could be sources of nitrites and nitrates. Excipient manufacturing can use potable and/or purified water. Typically, potable water has nitrite levels below 0.1 ppm and nitrate levels of 10 ppm and would not likely be a concern as a source of nitrosating agents.[12] 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 and nitrates.

As stated previously, nitrites are common precursor for nitrosating agents that have been reported in many excipients at ppm levels.[14] While nitrites are present in commonly used excipients at ppm levels, removing nitrites from excipients 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 components in the drug product formulation.

So, is it necessary to introduce limits for nitrites in excipients? In general, no, for the following reasons:

- Implementing general limits for nitrites will not alleviate the risk of nitrosamine formation
- The amount of nitrite present in a drug product as a result of an excipient is dependent upon the amount of excipient used in the formulation

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 (at any level) is a risk for nitrosamine formation. In such cases, 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.

Vulnerable Amine Containing 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 nitrosamine or a reactive amine that can convert to a nitrosamine within a drug product? Or are there excipients known to contain nitrosamines? An example of an excipient that is known to contain a nitrosamine as an impurity is trolamine (triethanolamine) and the nitrosamine impurity is N-nitrosodiethanolamine. In the European Pharmacopeia, the limit for N-nitrosodiethanolamine is established at 24 ppb.[15] While this particular excipient may contain a nitrosamine impurity, in general, the risk of an excipient introducing a nitrosamine directly to a drug product is negligible.

Amino acid excipients (e.g., L-histidine, L-proline, L-arginine) and other vulnerable amine containing excipients (e.g., triethanolamine, considering diethanolamine being present up to 0.5% as by-product of the synthesis) have the potential to react with nitrosating agents and form nitrosamines within the drug product, especially for biologics where the final drug product is routinely a solution formulation. While nitrosation of amino acids are possible, it has been reported in the literature that these nitroso compounds are not carcinogenic.[16-20] Similar to nitrites, the potential risk that may come from a

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vulnerable amine present in trace amounts in an excipient will depend on the formulation composition and should be evaluated accordingly.

Responsibilities of Excipient Suppliers

As the previous sections highlight, nitrosating agents and vulnerable amines may be found in 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, depending on the region. So, how should excipient manufacturers and/or suppliers support MAHs with global supply chains with their risk assessments? First, it should be made clear that excipient manufacturers are under no specific regulatory requirement to provide risk assessments on nitrosamines to regulatory agencies. However, 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. When levels of nitrites or vulnerable amine impurities are known to be present in an excipient, that information should be provided to the drug product manufacturer, drug product distributor, and/or MAH, by the excipient manufacturer or supplier.

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 have substantial databases of information on nitrosamines. 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 formation of nitrosamines 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

IPEC-Americas and IPEC-Europe have developed questionnaire templates 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 these templates or similar formats to inform drug product manufacturers. While each template is different, either one can be used as a starting point for providing excipient information to customers. These templates are publicly available on the respective regional IPEC website (IPEC-Americas Template, IPEC-Europe Template).

Reasonable Expectations / Misperceptions

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 manufactures 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

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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.

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.

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. 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. The excipients can also be a potential source for vulnerable amines (present in the chemical structure such as amino acids) that can undergo a chemical reaction with trace amounts of nitrites to form nitrosamines in the drug product. It should not be assumed that the presence of nitrites or vulnerable amines in an excipient will automatically lead to nitrosamine formation as this would be dependent on the API and formulation components. Additionally, specific reaction conditions are needed (i.e., low pH, elevated temperature, etc.) for the formation of nitrosamines to occur. Care should be given when excipients are evaluated as an input for the drug product nitrosamine risk assessment to ensure proper conclusions are made. 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.

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-containing components in an excipient does not necessarily lead to the formation of nitrosamines in a drug product. However, as components of excipients may contribute to the formation of nitrosamines in the final drug product, excipient suppliers should carefully evaluate the potential risk related to its excipients to assist drug product manufacturers to fulfil their regulatory obligations in conducting risk assessments for their drug products. 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. Therefore, IPEC supports the current focus of regulations on the drug product rather than requiring risk assessments or data from excipient manufacturers to be provided to the regulatory agencies.

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Future mitigation strategies should be focused on prevention of nitrosamine formation in drug products. Currently, excipients are viewed as risk factors for consideration during the drug product risk assessment. However, there are opportunities to explore the use of excipients as nitrosamine inhibitors in drug formulations. The FDA recently provided updates on possible strategies to reduce the risk of nitrosamine impurities in drug products.[22] 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 recently presented by Nanda.[21] The inhibition of nitrosamine formation in drug products may be possible with the careful evaluation of suitable inhibitors and excipients. However, for existing approved drug products this likely is a major investment and not a short-term solution.

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