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White Paper

Regulatory Considerations for Excipients used in Lipid Nanoparticles

Lipid excipients and delivery systems such as lipid nanoparticles (LNPs) are essential for a wide variety of therapeutic applications including chemotherapy, analgesics, cell and gene therapy, respiratory and ocular applications, anti-fungal applications, and vaccines (see **Figure 1**).[1] In many cases, these excipients and delivery systems play an important role in achieving the desired bioavailability. mRNA vaccines, for example, require incorporation of lipids to prevent degradation of the nucleic acid and facilitate cellular uptake of the mRNA which is required for antibody generation (see **Figure 2**).

The purity and safety of novel, synthetic lipid excipients must be demonstrated due to their central role in the function of the drug product, distinct physicochemical properties, and the potential for interaction with other ingredients or the physicochemical environment. These excipients must comply with challenging and complex regulatory requirements, similar to those expected of the active pharmaceutical ingredient itself.

This white paper provides an overview of the regulatory classification of lipid nanoparticles, liposomes and novel excipients. Specific requirements outlined in guidance documents are shared along with strategies to stay ahead of emerging regulatory challenges.

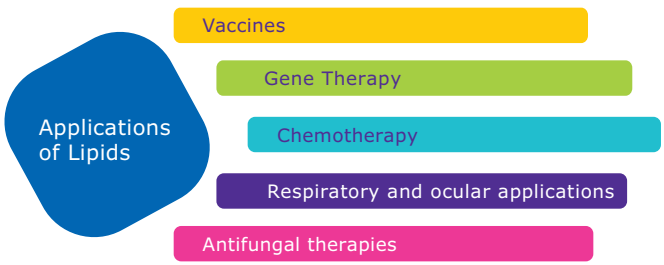

Figure 1. Lipids can be used for a variety of therapeutic applications.

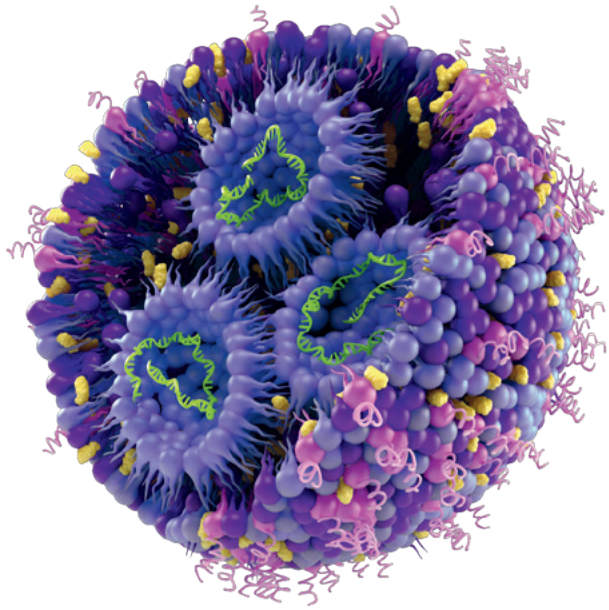

Figure 2. Lipid-based particles such as lipid nanoparticles (LNPs) are the most used delivery method for mRNA therapeutics and vaccines.

Excipient Types and Classification

For the appraisal of the regulatory expectations, the excipient is categorized into one of the following groups: compendial, non-compendial, co-processed, mixed, and novel.[2,3,4]

Compendial excipients meet the requirements of the pharmacopoeia while non-compendial excipients do not have any monograph in the pharmacopoeia. Co-processed excipients (CPEs) are manufactured by the physical co-processing of two or more excipients. During the co-processing no covalent bonds are formed. The properties of co-processed excipients cannot be achieved by blending or mixing of excipients. If two or more excipients are mixed, whereas they remain as discrete chemical entities, they will be classified as mixed excipients according to the International Pharmaceutical Excipients Council (IPEC).

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Novel excipients can be established or totally new chemical entities, as depicted in **Figure 3**. For lipid excipients the expectations from regulatory bodies are higher regardless of the class into which the excipient is classified.

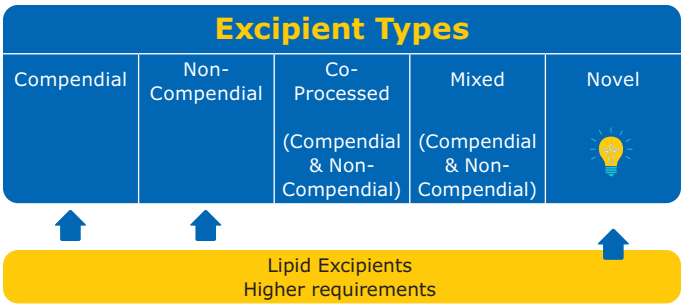

Figure 3. Excipient types according to IPEC Excipient Composition Guide.

As it is not entirely clear in some cases which scenario leads to the classification novel, the decision tree in **Figure 4** can be used as an aid. It can be seen that if there is no monograph and the excipient is a new entity, it is classified as novel. If it is not a completely new chemical entity but has not been used in human applications, it is also classified as novel. Similarly, the excipient is considered novel if it has been used in human applications but with a different dose and route of application. If the excipient is already used in human applications with a similar dose and route of administration, cross-referencing to another application from a similar excipient is possible as stated in the IPEC guidance.[3]

As the excipients is a vital part of the drug product, the excipient manufacturer is obliged to provide certain information which can be included in the drug product application. However, there is no uniform requirement for the filing of the regulatory information for lipid excipients in all countries as the regulations differ in various global regions (also depending on the compendial status of the excipient).

Regulatory Considerations

One of the most important aspects of excipients is their safety. For novel excipients a safety evaluation is required as well, which is quite extensive and time consuming. In most of the cases the already available data is sparse and therefore there is not much to which it can be referred to in bridging studies (depending on the "type of novelty" as shown in the flow chart in **Figure 4**).

Given these requirements, many excipient manufacturers concentrate on modifying existing excipients rather than developing entirely new ones. Regardless, the FDA guidance for lipid nanoparticles and liposomes points out that the requirements for lipid excipients are high whether the excipient is classified as novel or not.[5]

A potential reason for this perspective is the possible interactions between the lipid excipient and the active ingredient, the biological surroundings, and container closure systems. Because of the pivotal role of these excipients in the formulation, the documentation requires a high level of detail going far beyond that required for standard excipients.

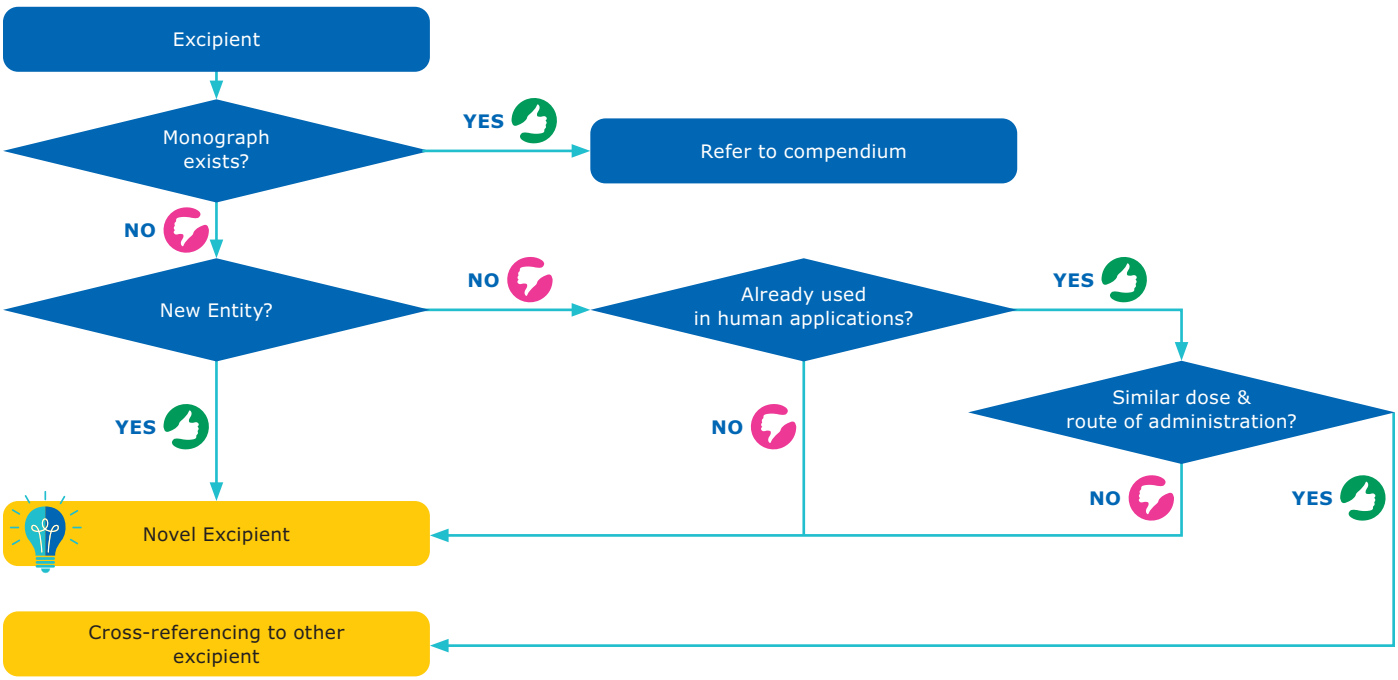

Figure 4. Decision tree for classification of a novel excipient.

Since the quality and purity of the lipids might have a significant impact on the quality of the final product, we experienced from filing procedures in the US and Europe that detailed information is required on the chemistry manufacturing and controls (CMC) of the lipid component. Therefore, it is important to identify critical process parameters during the process development. Furthermore, the evaluation of potential and actual impurities in the excipient plays a pivotal role in the excipient's safety and quality.

Impurity Evaluation

The control of impurities in lipid excipients is critical to ensuring their quality, safety, and suitability for use in pharmaceutical formulations. Unlike active pharmaceutical ingredients (APIs), lipid excipients are not governed by the impurity thresholds outlined in ICH Q3A.[6] However, impurity levels must still be carefully evaluated according to risk-based approaches and regulatory expectations, which may vary by region and application. While ICH Q3A is not applicable to excipients, elements of it can be used as a useful benchmark.

For lipid excipients, all relevant impurities should be identified and characterized based on their potential impact on the final drug product. Although specific thresholds for reporting and identification may not be universally applied, impurities that could affect the stability, efficacy, or safety of the formulation should be adequately controlled. In cases where certain impurities cannot be identified, a summary of laboratory efforts and any challenges encountered should be provided to demonstrate due diligence.

Total impurity levels must be evaluated, with appropriate documentation provided to demonstrate control over all significant impurities. Special attention should be given to categories of impurities that may have critical safety concerns, such as residual solvents (following ICH Q3C), elemental impurities (per ICH Q3D), and genotoxic impurities (per ICH M7), which may require more stringent controls depending on their potential risk.

A robust impurity control strategy helps manufacturers maintain the consistent quality of lipid excipients and ensures compliance with regulatory standards, thereby reducing risks in pharmaceutical formulations.

Residual solvents, used in the manufacturing process are controlled on a regular basis in the final product (according to ICH Q3C)[7]. For residual solvents that are known to negatively impact LNP formulations, lower limits may be applied. For the evaluation of the elemental impurities (according to ICH Q3D)[8], a risk assessment is performed which evaluates if elemental impurities are likely to occur in the product. The assessment of the mutagenicity of both potential and actual impurities is of central importance. Although ICH M7 formally applies to drug substances and drug products, the principles outlined therein may also be applied, where scientifically appropriate, to novel excipients.

Mutagenic impurities are categorized in classes 1–5 where class 1 is the most critical. During the assessment for genotoxic impurities, which his required as input for the impurity CMC section, a computational toxicology assessment (QSAR) is carried out. As consequence the potential and actual impurities of the excipient can be classified and potential mutagens identified. Upon identification of genotoxic impurities, degradation products must be identified using forced degradation studies and photostability studies as well as the influence of the packaging on the generation of genotoxic impurities. Within the scope of this evaluation, nitrosamines also play an important role as in some cases they can be assigned to class 1 (potent genotoxic agents). Nitrosamines are possibly introduced from different sources during the process, including raw materials. Furthermore, they can arise during the process from certain reaction conditions (e.g. pH or temperature). In consequence, the process needs proper control by experienced manufacturers.

The Value of an Experienced Partner

Therapeutics and vaccines that rely on lipids and lipid-based delivery systems offer the potential to treat and prevent diseases that cannot be addressed with traditional small molecule therapeutics or biologics. Development and manufacturing of these modalities, however, bring many challenges and your supplier should serve as a valuable partner to mitigate risk and help deliver a successful formulation.

There is a large diversity of lipids from which to choose and thoughtful design of the formulation is essential as the raw materials and formulation process are as important as the drug delivery method itself. Ensuring quality of raw materials with appropriately low impurity levels and the formulation is critical; inconsistent quality can lead to a lack of reproducibility, regulatory hurdles, high costs, and wasted resources. Similarly, selection of a supplier with a robust supply chain is also critical to ensure the necessary product quality and reliable delivery timelines.

The diversity and integral role of lipids also means that the associated regulatory expectations are stringent, intricate, and evolving. A partner with deep expertise in this space can help you confidently navigate the complexity, remain complaint, and support a successful commercialization.

Your CDMO partner

Bringing your lipid-based therapeutics to life takes more than experience, it takes passion. We're all in to simplify the journey of advancing your therapies to patients.

Choose from GMP-ready, fully connected services from lipid manufacturing through LNP formulation, manufacturing and Fill & Finish. Our global facilities and technical depth are designed to guide you seamlessly from early development through clinical and commercial scale.

We stay focused on helping you move forward, every step of the way. Together, We're All In.

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