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White Paper

Regulatory Considerations for Excipients used in Lipid Nanoparticles

Claudia Widmann, Regulatory Expert

Lipid excipients and delivery systems such as lipid nanoparticles (LNPs) are essential for a wide variety of therapeutics including chemotherapy, analgesics, gene therapy, respiratory and ocular applications, anti-fungal applications, and vaccines (see Figure 2).[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 1).

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.

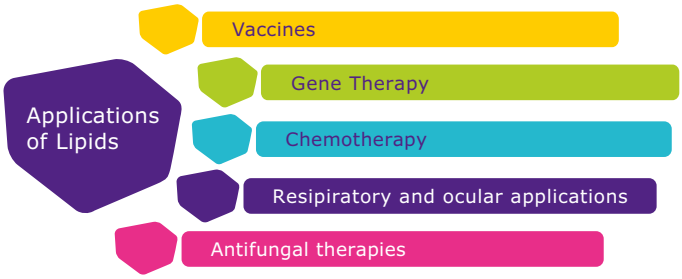

Figure 2.

Lipids can be used for a variety of applications.

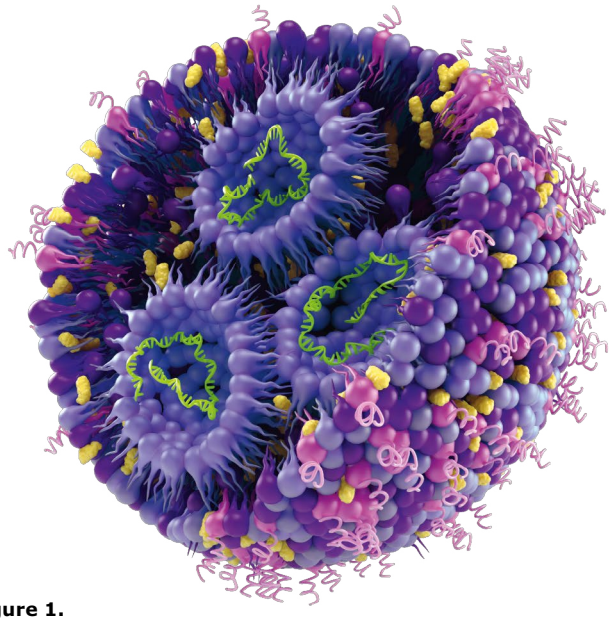

Figure 1.

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 can not 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.

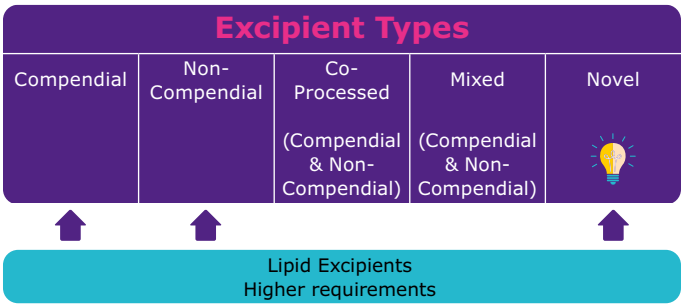

Figure 3.

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. In general, such excipients cannot be regarded as inert[6] and the level of detail that should be provided with the documentation is like that of an active pharmaceutical ingredient (which is similar to the requirements of novel excipients).

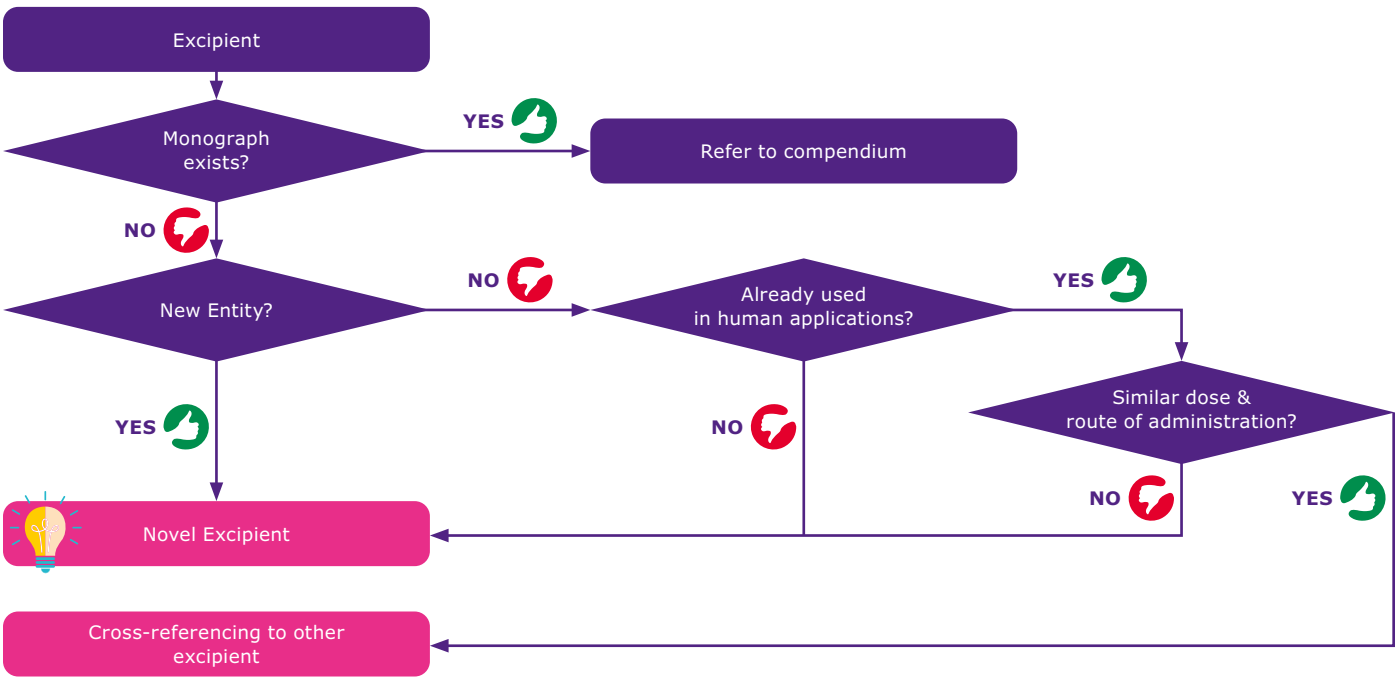

Figure 4.

Decision tree for classification of a novel excipient.

Since the quality and purity of the lipids can affect 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, whereas the impurity evaluation of potential and actual impurities in the excipient plays a pivotal role in the regulatory documentation.

Impurity Evaluation

For the control of impurities, different guidance documents from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) are available. In ICH Q3A, recommendations on impurities in general are provided.[7] Impurities that exceed the reporting threshold of 0.1% or 0.05% should be identified with the percentage used as a guideline depending on the applied daily dose. If the identification of the impurity is not possible, a summary of laboratory studies demonstrating the unsuccessful effort shall be included. Furthermore, impurities greater than the reporting threshold must be added together and reported as total impurities. To show the typical impurity profiles in the documentation, representative batch chromatograms need to be provided as well. Specific impurities which deserve special attention include residual solvents, elemental impurities, and genotoxic impurities.

Residual solvents, used in the manufacturing process are controlled on a regular basis in the final product (according to ICH Q3C)[8]. For the evaluation of the elemental impurities (according to ICH Q3D)[9], a risk assessment is performed which evaluates if elemental impurities are likely to occur in the product. Besides these well known ICH impurity guidelines, a evaluation of the genotoxicity of potential and actual impurities is of central importance. Therefore, genotoxic impurities need to be evaluated for novel excipients[10] and lipid excipients being subject to new marketing applications for example.

Genotoxic 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 can't 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.

Selecting a CMO Partner

An experienced contract manufacturing organization can provide invaluable support for RNA therapeutic and vaccine formulation, quality lipids and LNP manufacturing. Selecting the right partner, early in your process, can provide a competitive advantage and accelerate development and manufacturing. Our organization is well-versed in the development and manufacturing of GMP lipids and has a strong technical and regulatory team with more than 85 years of combined experience. Developers of RNA-based therapeutics can select from an extensive portfolio of lipids or opt for custom manufacturing. We are experienced in the manufacture of ionizable lipids, PEGylated lipids, and targeted lipids, with manufacturing sites around the world that are regularly audited by regulatory authorities and customers.

During the COVID-19 pandemic, when so many RNA-based vaccines were being developed, the industry was in urgent need of a large supply of lipids. We had the appropriate network, expertise and supply capabilities within our global organization to support companies developing vaccines from the earliest days of the pandemic. More than 50 companies have collaborated with us to support their efforts in the development and production of COVID-19 vaccines and treatments.

In February 2021, we announced the extension of our strategic partnership with BioNTech to significantly accelerate the supply of urgently needed lipids and increase the quantities to be delivered toward the end of 2021. The lipids are used for production of the Pfizer-BioNTech COVID-19 vaccine.

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Merck KGaA
Frankfurter Strasse 250
64293 Darmstadt
Germany

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