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Active ingredient vs excipient debate for nanomedicines

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Nanomedicines are complex drugs where components that have typically been regarded as excipients may now be considered part of the active ingredient. The distinction between the active ingredient and excipients for nanomedicines has important consequences for regulatory review and product development. The dissimilarity in the review of the recent ribonucleic acid (RNA)-based lipid nanoparticles highlights the need for further regulatory alignment on this topic.

The nanomedicine field is witnessing a steady increase in the transition of formulations from proof-of-concept into clinical trials[1,2]. The proven capabilities of nano-formulated drugs include enhanced pharmacokinetics (for example, longer half-life) and decreased toxicity profiles when compared to their traditional counterparts. Recent drug approvals have now extended this success to the formulation of novel compounds, such as the mRNA lipid nanoparticles (LNPs) in the COVID-19 vaccines[3]. As the developers for these drugs enter the preclinical stage, their attention turns to mapping out the most appropriate regulatory strategy for their product. To aid with this journey, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have produced helpful guidelines. These documents, some specifically related to nanomedicines, provide the drug developer with a framework for selecting the appropriate regulatory path towards clinical trials and eventual product approval. The relevant pathway will then determine the type and amount of data that will be required for regulatory review. For example, a novel drug will likely require full Phase I to Phase III clinical trials, whereas a nano-formulation of an existing drug may qualify for an abridged/abbreviated review or as a generic formulation[4,5].

Exploring these pathways a little deeper, the nanomedicine drug developer is soon confronted with an ongoing debate in Regulatory Science. Namely, the ambiguities surrounding the definitions of the active ingredient and excipients for nanomedicines. We proffer here that this debate is far more than a nuanced discussion on regulatory terminology, but rather has significant impacts on product development and regulatory dossier preparation and review.

Understanding the components of nanomedicines

The majority of approved nanomedicines consist of an active ingredient that is encapsulated or otherwise incorporated into a nanoparticle vehicle, made of inactive ingredients (excipients) such as lipids, polymers and carbohydrates. According to Title 21 of the US Code of Federal Regulations (21 CFR) and Directive 2001/83/EC of the European Parliament and of the Council (as amended by Commission Directive 2011/62/EU) the terms active substance/active ingredient and excipient/inactive ingredient have formal definitions (Table 1).

Table 1 | Definitions for active substance/active ingredient and excipient/inactive ingredient

Term	EU	USA
Active substance/active ingredient	Active substance is any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.[a]	Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.[c]
Excipient/inactive ingredient	Excipient is any constituent of a medicinal product other than the active substance and the packaging material.[b]	Inactive ingredient means any component other than an active ingredient. [d]

[a]Article 1(3a) of Directive 2001/83/EC, as amended by Commission Directive 2011/62/EU, [b]Article 1(3b) of Directive 2001/83/EC, as amended by Commission Directive 2011/62/EU, [c]21 CFR 210.3(b)(7), [d]21 CFR 210.3(b)(8).

For the purposes of this article, we will use the terms (active) drug substance and active ingredient interchangeably. Within FDA's Guidance Document for products that contain nanomaterials[6] the definition for excipient is broaden to: "…an excipient is any inactive ingredient that is intentionally included in a drug product, but that is not intended to exert therapeutic, prophylactic, or diagnostic effect(s) at the intended dosage, although it may act to improve product delivery (e.g., enhance absorption or control release of the drug substance). Excipients (e.g., polymers, targeting agents, coating agents, and lipids) in some cases are also used as matrices to assemble structures or to stabilize more complex nanomaterials."

Herein lies the ambiguity between the classification of excipients and active ingredients for nanomedicines. Namely, the definition of excipients excludes those components that exert a therapeutic effect.

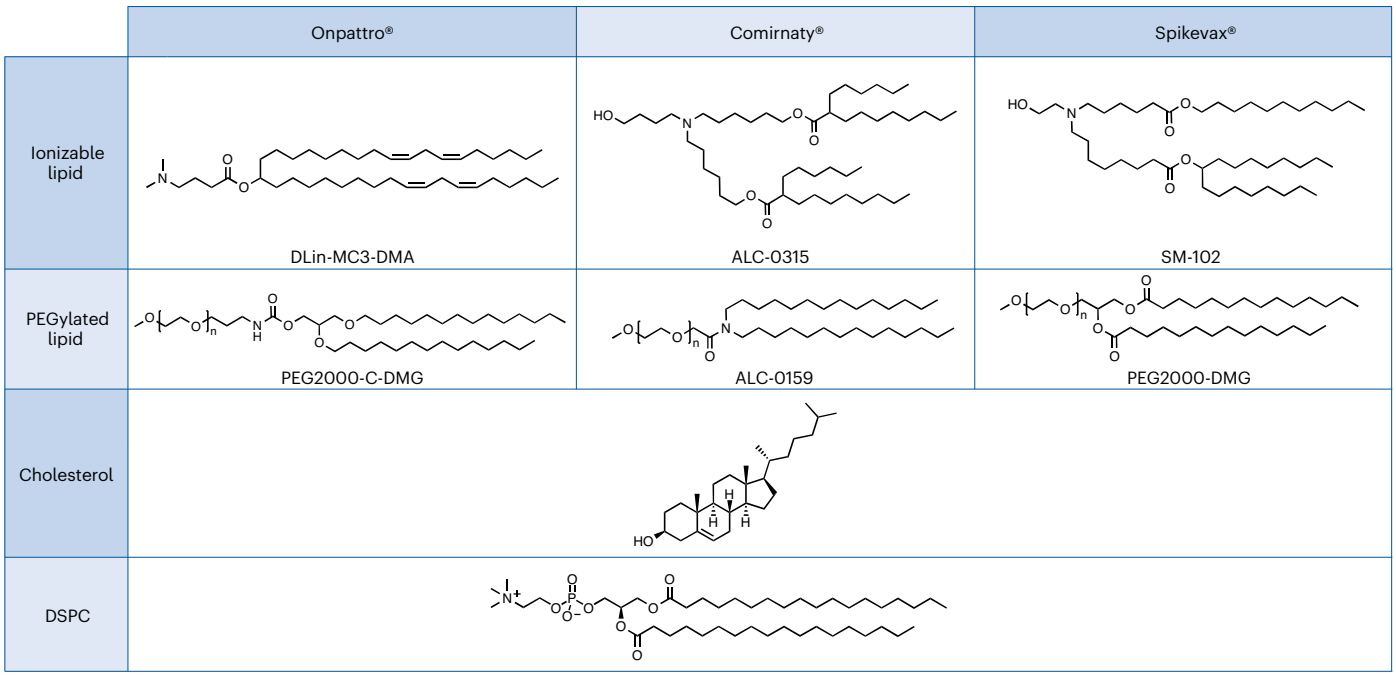

Fig. 1 | Similar LNPs in Onpattro, Comirnaty, and Spikevax. LNPs used in Onpattro, Comirnaty, and Spikevax share several characteristics. Specifically, all three products are made up of a combination of four different lipid types. Two of these lipids, namely cholesterol and DSPC, are identical for all three products. The other two lipids are ionizable lipids with a tertiary amine group and PEGylated-lipids, which are similar for all three products. Overall, the LNPs in the three products share a resemblance in composition and structure.

For nanomedicines, however, all components of the nanoparticle will contribute to the efficacy and safety profiles of the final drug product. Liposomal formulations of doxorubicin, for example, have decreased cardiotoxicity compared to legacy drug (adriamycin)[7] and the lipids within the mRNA LNPs aid in endosomal escape, and subsequently play a key role in efficacy[8]. The properties of the active ingredient may therefore be different when incorporated into a nanoparticle, leading to modified behaviours in the body[9].

Should the composite nanoparticle be considered as the active ingredient?

The discussion above leads to the question of whether the nanoparticle itself should be reviewed by regulatory authorities as the active ingredient, and how to accordingly define the active ingredient, excipients, and the final drug product. One can make the scientific case that the composite nanoparticle is the de facto active ingredient as all components contribute to "…pharmacological activity or other direct effect." This approach is already supported by monographs from the United States Pharmacopeia and the European Pharmacopoeia for certain nanomedicines (for example, iron sucrose) since the active ingredient and excipients simply cannot be distinguished from one other[9].

The active ingredient vs excipient question has several implications for the drug developer during the preclinical stage. It is a given that a developer must demonstrate the safety of a new active ingredient used in a nanoparticle that has not previously been approved. However, per the current guidelines, a novel lipid or polymer requires a comprehensive non-clinical development program equivalent to that required for introducing a new active ingredient, including expensive toxicological evaluation[10]. This type of componentwise in vivo evaluation is not simply a cost issue but can also delay clinical trials, as excipients intended for long-term use may require 6-month repeat-dose toxicology studies and 2-year carcinogenicity studies.

The drug developer must of course have firm and convincing data that their particular nanomedicine is stable – that it can sustain its integrity in biological fluids, whilst still maintaining its therapeutic effect. For such stable nanomedicines, componentwise evaluation may lead to misleading data and findings. Nanoparticles greater than approximately 8 nm in size, for instance, are primarily cleared from the bloodstream by the mononuclear phagocytic system (MPS)[11]. The individual lipids and polymers, in contrast, will likely have different routes of clearance, different pharmacokinetic and biodistribution profiles if evaluated separately from the intact nanoparticle[12]. Similarly, evaluating a novel active ingredient without the protection afforded by encapsulation in a stable nanoparticle, may exhibit off-target adverse side effects. Naked nucleic acid-based active ingredients, as an extreme example, will result in severe immunotoxicity if systemically administered as reviewed by Bila et al.[13] and Johnson et al.[14]. One can also make the case that piecemeal in vivo evaluation of a stable nanomedicine is not in alignment with the '3 Rs principle (replacement, reduction, refinement) in animal experimentation' as it does not prioritize the responsible use and reduction of animals[15].

Case study of three RNA-based nanomedicines

A pertinent case study for the above premise, which also highlights a dissimilarity in regulatory review, can be found in the recent approval of ribonucleic acid (RNA)-based nanomedicines. Closely related LNPs have been used as the delivery system for the following three RNA drugs: Alnylam's RNAi-based therapy for the treatment of hereditary

transthyretin (hATTR) amyloidosis (trade name: Onpattro); the Pfizer–BioNTech COVID-19 vaccine based on mRNA technology (trade name: Comirnaty); and the Moderna COVID-19 vaccine (trade name: Spikevax), also based on mRNA technology. The individual components of the three LNP products are very similar (Fig. 1.)[16]. In brief, the LNPs are comprised of an ionizable cationic lipid, a PEGylated lipid, cholesterol, and a structural lipid (distearoylphosphatidylcholine; DSPC).

All three drugs are approved by the FDA and the EMA. Yet despite having very similar LNP compositions, Spikevax's LNP components were classified differently by the applicant. This classification was accepted by the FDA, and consequently, Spikevax LNP was reviewed differently than the cognate LNPs in the other two products. We compare and contrast the respective regulatory dossiers below. For EMA these details are found in the European Public Assessment Report (EPAR), and for the US FDA, the information is contained in the publicly accessible review and approval documents (FDA approval letters, product labels, Summary Basis for Regulatory Action and Review Memoranda).

Onpattro. According to EMA, the Onpattro drug product is an LNP formed by a mixture of four lipid excipients that encapsulate the double-stranded siRNA (ds-siRNA) patisiran sodium (active substance). Two of the lipids, DLin-MC3-DMA and PEG2000-C-DMG, are considered novel excipients[17]. The US FDA similarly considers the four lipid components forming the LNP as excipients, with DLin-MC3-DMA and PEG2000-C-DMG also designated as novel[18].

Spikevax. In the initial submission of their regulatory dossier, Moderna declared the mRNA and the lipid components as the drug substance[19]. During EMA's review of this first version, it was pointed out that only the mRNA should be considered as the active substance. The Spikevax dossier therefore had to be amended to be in line with EU requirements, since EMA regards all four lipid components of the LNP as excipients. Two of these are considered novel, namely, SM-102, an ionisable lipid excipient, and the polyethylene glycol-lipid conjugate, PEG2000-DMG (ref. 19).

In contrast to EMA's review, FDA accepted Moderna's classification of PEG2000-DMG and SM-102 as 'starting materials' for the drug substance, rather than as excipients[20] and the regulatory dossier remained structured accordingly. The full list of excipients does not include PEG2000-DMG and SM-102 (nor the two remaining lipids) and the Chemistry Manufacturing and Controls (CMC) BLA Review Memorandum explicitly states that the mRNA-1273 drug product does not contain any novel excipients. FDA's summary basis for regulatory action also lists the LNP under the description of the active ingredient[21]. Juxtaposed to its own ruling in the CMC section, FDA's toxicology review for Spikevax[22] identifies SM-102 and PEG2000-DMG as 'inactive ingredients', hence regarding SM-102 and PEG2000-DMG as excipients rather than starting materials for the drug substance.

Comirnaty. Consistent with their review of Spikevax, EMA considers Comirnaty's structural lipids DSPC and cholesterol and functional lipids ALC-0315 and ALC-0159 as excipients, with the latter two being considered as novel[23]. In contrast to this, and to its ruling on Spikevax, FDA states that Comirnaty contains four pharmacologically inactive lipid excipients. Namely, DSPC, cholesterol, ALC-0159 and ALC-0315, with the latter two described as novel excipients[24]. According to FDA's summary basis for regulatory action, the four lipids forming the Comirnaty LNP have a function of a 'lipid component' whereas all other ingredients, also supposedly inactive ingredients, are considered as excipients[25].

In short, the FDA reviewed the lipids in Spikevax as part of the drug substance, whereas very similar lipids in Onpattro and Comirnaty were reviewed as excipients. EMA was more consistent in their review, as the lipids in all three LNPs are listed as excipients. We emphasize here that our case study for these three LNPs does not assess the proprietary data provided in the regulatory dossiers, and is limited to publicly available information.

The nanomedicine active ingredient: charting the way forward

Alignment and further clarification on the classification, terminology, and regulatory criteria related to nanomedicines will help mitigate regulatory risk, and bring efficacious and safe therapies to patients faster. FDA's ruling on the Spikevax case sets a regulatory precedent for classifying the composite nanoparticle as the active ingredient. It represents an important reference point for the regulatory dossier preparation by companies developing nanomedicines and the subsequent assessment of these formulations by regulators.

It is important to emphasize that each nanomedicine is unique, and one cannot simply expect the FDA and EMA to issue blanket statements on the active ingredient vs. excipient topic. The regulatory agencies do encourage drug developers to meet with them as early as possible in the development process, and certainly prior to submitting documents for regulatory review. This is to answer regulatory-related questions and aid with project planning. These interactions usually pertain to the specific product, however, and are conducted under confidentiality.

As an additional conduit, the field of Regulatory Science facilitates the transparent and collegial discourse among regulatory bodies, drug developers, academicians and other stakeholders on matters such as the topic presented here. In this regard, we respectfully propose that the composite nanoparticle be ruled as the active ingredient for stable particles, and that the evaluation of excipients/inactive ingredients be limited to those that are truly inactive.

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Competing interests

S.M. is a member of the Non-Biological Complex Drugs (NBCD) Working Group (convened by Lygature, Netherlands), and the Chair of the NANO working party at the European Directorate for the Quality of Medicines & Health Care (EDQM). He also serves as a paid scientific consultant for CSL-Vifor (Switzerland) and for InnoMedica Holding AG (Switzerland).