Lipid nanoparticle–based COVID-19 vaccines: Concerns about stability

According to a US Government Accountability Office (GAO) report to Congress published in early 2021, GAO found "that agencies are working to help mitigate vaccine manufacturing challenges. . ." in the fight against coronavirus disease 2019 (COVID-19), including efforts "to prioritize vaccine production supplies."[1] Around the same time, similar calls for attention to vaccine production and distribution program implementation were made.[2] Moreover, the authors of the GAO report pointed out that the Food and Drug Administration (FDA) established a minimum efficacy threshold, ie, a primary efficacy endpoint estimate of at least 50%, to ensure vaccine efficacy. As well, others have cautioned that the shortened development time, plus the novel technologies applied, likely means COVID-19 vaccines have been deployed with several unresolved issues, so they may need future refinement.[3]

Although much of the attention has been rightfully focused on production scale-up and distribution, very little attention has been paid to the physical stability of the lipid nanoparticle (LNP) dispersions. The available LNP-based COVID-19 vaccines have 2 critical components: functional lipids affecting the active pharmaceutical ingredient (API) and structural lipids affecting the stability of the dispersion. In fact, significant differences in chemical instability of the API (defined as "% mRNA integrity/truncated species") were noted between clinical and proposed commercial batches.[4] By comparison, and depending upon the therapeutic index of the drug, official pharmacopeial limits for an FDA-approved API are generally ±10% of the labelled amount. Also, there is no official consensus as to the best physical method(s) to assess the stability of LNP dispersions.[5] At the moment, the closest pharmacopeial standard is USP general chapter 729 (USP <729>),[6] but the limits are based on phospholipid-stabilized, homogenized triglyceride oil droplets in water (ie, Lipid Injectable Emulsions, USP), where the mean droplet diameter, or MDD, needs only to be no more than 500 nm. In contrast, LNP dispersions have an MDD about an order of magnitude lower[7] than that specified in USP <729>, so at this time there is no official method or guidance that applies to LNP dispersions.

For all FDA-approved drugs, there are chemical limits for each API given by the labelled amount. For certain dosage forms, such as Propofol Injectable Emulsion, USP, there are also required physical tests to verify the integrity of the drug delivery vehicle while recognizing that the stability of the colloidal dispersion may also assume clinical significance. This concern might also be relevant to LNP-based COVID-19 vaccines. The stability of the particle size distribution (PSD)—particularly the large-diameter, "outlier" tail of aggregates—signals major physical stability issues, which have clear implications for the structural lipids maintaining the colloidal dispersion. These oversize particles also significantly alter the homogeneous distribution of the API within the functional lipids in the pharmaceutical dosage form. Consequently, the resulting imprecise and inconsistent delivery of sufficient amounts of the vaccine may affect clinical outcomes.

Fortunately, the requisite technologies are available to determine the LNP particles of interest in the deep-submicron size range.[8] Importantly, quantifying changes in the oversize tail of the PSD of dispersions is necessary for any assay that is stability indicating. Now that numerous batches of these vaccines have been produced and administered, along with the recognition that mRNA LNP–based vaccines are a "true platform technology,"[7] pharmacopeial requirements should now be expanded to establish official particle size limits for LNPs similar to the parameters (ie, mean particle size and large-diameter PSD tail) previously established for lipid injectable emulsions in USP <729>.

1. US Government Accountability Office. *Operation Warp Speed: Accelerated COVID-19 Vaccine Development Status and Efforts to Address Manufacturing Challenges.* US Government

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