Drivers for Vaccines and Lyophilization of Product

The driving force for choosing between a liquid image and a lyophilized image is mainly linked to the stability and storage requirements within the GTPP. Lyophilization has the advantage over liquid images in terms of stability, storage, and ease of shipment for clinical development and marketing, especially with the desire to move into new emerging and developing world markets where increased thermal stability is highly desired [10].

Another advantage and driver for products to move to a lyophilized form is that lyophilization normally meets the product sterility assurance without terminal sterilization due to the process being a trusted aseptic operation [10]. For biopharmaceuticals, lyophilization is the industry benchmark for attaining a dried product, and any deviation or innovative approach to obtain dried product will have the burden of overcoming the technology barrier while maintaining comparable (if not superior) quality assurance as the lyophilized product [11].

Lyophilized products, especially vaccines and biologics, add an additional benefit when a multidose image may be required. Most vaccine products are incompatible with preservatives, and thus, achieving the required stability profile in the liquid state is unobtainable when in a preservative-containing formulation. By lyophilizing the vaccine without a preservative, the negative stability effects associated with the preservative, can be removed form the product. This is achieved by having the preservative be part of the reconstitution diluent and minimizing the exposure of the vaccine to the preservative. Thus, long-term stability of the vaccine is not impacted.

In addition to improving the success for a preservative-containing vaccine, there are instances where vaccine antigens may need to be detoxified. One common approach for detoxification is the use of formaldehyde. However, long-term liquid stability with a formaldehyde product may not be feasible due to the potential for reversion. To overcome this, lyophilization can be utilized to mitigate reversion to toxicity [12].

Finally, lyophilization of live virus vaccines (LVV) is usually necessary to achieve the desired long-term stability profile. Unlike protein-based vaccines, LVV (enveloped and non-enveloped) are significantly challenging in their intrinsic thermal stability [13]. Liquid degradation rates for LVV can be as high as 10% per hour in the liquid state at refrigerated temperatures. Thus, achieving a stable liquid formulation for an LVV is usually not obtainable, and thus, necessitates the use of lyophilization to achieve a vaccine that is safe and efficacious over the desired shelf life of the product [13].

Although there are some potential benefits associated with a lyophilized vaccine product, the freeze-drying process does have some disadvantages [10, 14–16]. These include the additional unit operation of lyophilization, higher cost with manufacturing, large capital investment in equipment, the potential impact of freezing and drying stresses, inability to lyophilize an aluminum-based vaccine, and differences in equipment across laboratory, pilot, and commercial scale when developing a robust process. As the formulation scientist initiates vaccine development, the scientist must assess the GTPP and determine how best to achieve the desired