from the collapsible blister by an attached Luer port. Alternate configurations include the needle as well.

This and related technologies can be found in the patent literature. Designs are under development, and are currently undergoing testing by major pharmaceutical companies.

Reformulation as Liquid

The basic rationale for freeze-drying pharmaceutical dosage forms is to protect the active moiety from hydrolytic degradation when in solution. Early in the drug development cycle, the amount of drug substance available to pharmaceutical development teams is typically very small—often less than a gram. The first priority for the pharmaceutical development team is to provide a formulation for the toxicologist. If the active principle is susceptible to hydrolysis, extra efforts at developing a liquid formulation are often deferred for a quick freeze-dried product in a vial. Soon the project transitions to phase I clinical trials, and as often happens the switch to a potential liquid formulation gets low priority for resources and funding. Liquid products are obviously less expensive, and find greater acceptance in the clinic because of ease of use.

A number of freeze-dried products have transitioned to liquid solution products post approval. These include gentamicin, human growth hormone, docetaxel, gemcitabine, bendamustine, doxorubicin, and epirubicin. The conversion of these freeze-dried products to solution was primarily based on finding optimal solution parameters like pH, osmolality, ionic strength, protection from oxygen, and sometimes choice of more suitable excipients, etc. A multifactorial study designed to find the optimum conditions for stability can be pursued to this end.

Yet another approach to liquid formulations has evolved with the advent of encapsulation technologies. These technologies include liposomes, lipid complexes, and emulsions. As is well known, liposomes and lipid complexes are made of phospholipid bilayers, with the tails of the phospholipid molecules aligning to form a hydrophobic region. If the active drug is hydrophobic (or using the base of the active drug instead of the salt) the drug can be "trapped" in the hydrophobic region. Often this is adequate to protect the drug from hydrolytic degradation—even though the hydrophobic region of the bilayers is not completely "walled off" from the aqueous milieu.

One of the best examples of this approach is Abelcet, a lipid complex formulation of amphotericin B. This product is a liquid formulation, refrigerated. Considering that the original amphotericin B formulation (Fungizone) is a freeze-dried product, which needs refrigerated storage conditions for stability, the Abelcet lipid complex liquid formulation is a huge advantage. It is important to remember that reformulating a freeze-dried product in a lipid matrix changes its pharmacokinetics, pharmacodynamics, bio-distribution, and safety and efficacy profiles. Thus, this approach invariably demands complete preclinical and clinical studies.