necrosis factor formulations (13). One of the conclusions drawn from the study was that oil droplets promoted growth of particles by adsorbing to them, thus allowing sites for additional particle growth.

Testing for Silicone Oil

The presence of silicone oil on closures can be easily identified qualitatively through infrared (IR) spectroscopy. Typically strong bands are found in the 1200 to 1000 cm^{-1} region, near 2900 cm^{-1} with additional sharp bands in the 1270 to 1250 cm^{-1} and 874 to 740 cm^{-1} regions. A quantitative method for understanding the amount of silicone oil applied to the closures is required to determine optimization of silicone oil application. This can be conducted through a quantitative IR method or through atomic absorption methods. In both cases, the silicone oil is removed from the stoppers with an organic solvent. The amount of silicone oil is then quantified in the solution by comparing the samples to predetermined standards and calibration curves.

These methods can be used to assist in silicone level and application optimization.

Methods have also been developed to quantify the amount of silicone oil in some drug products or placebos. Typically atomic absorption is used following a liquid/liquid extraction of the drug solution. These methods are valuable in helping to analyze the cause of a hazing or leaching problem.

Alternatives to Silicone

For many years silicone oil was the only material added to closures for lubricity purposes. Closure manufacturers have developed several alternatives to the traditional silicone oil that can be used in a similar function. The alternatives range from a cured silicone that is retained onto the closure surface better than traditional silicone oil, to films that are based on fluoroelastomer polymers. Each of these alternatives can be beneficial. Their use helps avoid the need to optimize silicone application by the drug manufacturer and, in some cases, such as with the film coatings, additional benefits in areas such as reduction of extractables is typical.

CONTAINER CLOSURE SYSTEMS

One extremely important feature of the entire package is its need to keep a seal after the lyophilization process. Many features have to come together to achieve this in a satisfactory manner. This is more of a challenge for a lyophilized product than a liquid injectable because the seal must be maintained for several hours without the application of the aluminum overseal. The elastomeric formulation, the closure shape, any closure coating, and the glass vial all must fit together perfectly to achieve the required sealing characteristics. The fit between the rubber and the glass is critical. The use of, for instance, a rubber formulation that is too hard may cause a problem because harder formulations become less elastic. Closures with coatings must be evaluated carefully. The addition of a coating may increase surface hardness or may, depending on its area of application, become a barrier between the glass and the rubber. This barrier or increase in hardness prevents the rubber from sealing adequately, especially where there may be nicks or lines in the surface of the glass vial finish. If the