

## Impact of leachables from prefilled syringe components

Leachates and their impact on protein drugs, especially when filled into prefilled syringes, have become a major concern for regulatory agencies (Nashed-Samuel, Liu, Fujimori, Perez, & Lee, 2011). Some of this stems from the lessons learned from erythropoietin (EPO), specifically Eprex<sup>®</sup>, that was initially in vials and then filled into prefilled syringes. In addition, the route of administration was changed from IV to SC, and a formulation change was made from human serum albumin to polysorbate 80. These changes resulted in an increase in pure red cell aplasia (PRCA) whereby an immunogenic response not just from the drug, but also to the patient's endogenous EPO resulting in an inability to make red blood cells (Casadevall et al., 2002). It has been suggested that leachables eluting from the stopper in the prefilled syringe are adjuvants that stimulate the immune system (Boven et al., 2005). This conclusion has been questioned since the leachates had an adjuvant effect when administering ovalbumin, but not for Eprex<sup>®</sup> (Schellekens & Jiskoot, 2006). An alternative explanation was proposed where micelles from the polysorbate 80 generated aggregated EPO. However, the final conclusion was that many things were changed at the same time, and thus it is difficult to determine what was the single cause for the increased PRCA (Locatelli, Del Vecchio, & Pozzoni, 2007). Although the exact cause for the increased PRCA is not known, the observation that leachates were extracted from the uncoated stoppers in prefilled syringes (Pang et al., 2007) has made leachates a major concern. Although plastic syringes appear to be a good alternative to glass syringes since silicone oil is not needed, there are concerns regarding potential leachates from the plastic surfaces (Jenke, 2007).

## Potential interactions with stainless steel needles

The stainless steel in needles is usually constructed from 304 stainless steel. The 300 series are prone to pitting corrosion in the presence of chloride ion, and this may be a long-term concern for mAbs that are in contact with the needle surface for extended periods of time. Although this has been a concern, there are several products in prefilled staked needle syringes that have significant amounts of chloride ion (Table 8.1).

A study was conducted using an IgG<sub>1</sub> mAb to determine whether or not the corrosion of a stainless steel needle in the presence of a mAb formulated with chloride ion was an issue. Prefilled mAb syringes were stored at 2–8°C for ~7 months. The wetting of the needles was assessed by inserting a stainless steel wire into the needle and sealed with silicone glue (Dow Corning 3140). Since the mAb formulation is conductive, any liquid contacting both the syringe needle and the end of the stainless steel wire could be measured by using an external electrical excitation. A Radiometer Analytical Voltalab 30 potentiostat configured for impedance measurement was used to determine the wetted state of the wired syringes and the degree of wetting of the stainless steel needle surface. In order to determine if silicone oil could protect against potential pitting, 316L stainless steel coupons with and without silicone oil coatings were assessed for potential electrochemical pitting. Also the extraction of metal from