LEACHABLES FROM SINGLE-USE SYSTEMS AND IMPACT TO PRODUCT QUALITY

Nina Xiao, Genentech Inc.
njxiao@gene.com
Adithi Chandrasekhara, Genentech Inc.
Miguel Saggu, Genentech Inc.
Ed Hoff, Genentech Inc.
Ankit Patel, Genentech Inc.

Key Words: Single-use, gamma irradiation, protein aggregation, particles

Application of single-use (SU) systems for the manufacturing of biologics have increased significantly over the years and pose challenges for pharmaceutical processing in terms of leachables and their potential impact on product quality.
Our small-scale stressed/accelerated studies (conducted at ≥ 25°C with elevated surface area to volume ratio) revealed increase in protein aggregation and sub-visible particles resulting from storage in disposable bags compare to other non-disposable storage containers (glass vials and stainless steel). Three classes of relevant leachable compounds are believed to potentially interact with protein and promote protein aggregation. We have repeatedly shown that some of the protein aggregates are dissociable by SDS and preventable by increasing polysorbate 20 levels (indicating hydrophobic leachable compounds). We have also observed covalent protein aggregates that are preventable by adding anti-oxidants (suggesting leachable compounds that promote strong protein crosslinking). Furthermore, we have observed protein aggregates that can be prevented by heat-treated bags prior to storage (indicating volatile compounds).

In addition to protein aggregation observed in SU bioprocess bags, our lab-scale studies have shown that visible protein particles could form readily upon contact with gamma irradiated SU assemblies used for filling drug product (DP). Gamma-irradiated silicone tubing and lynx connectors (taken from assembly) generated substantial amount of particles (majority non-protein and some protein) that would not be acceptable if observed in the final DP. No apparent impact of formulation parameters have been found in these studies.

Localized discoloration of silicone tubing was observed around areas with PVC cap (used as a guard on the pinch clamps) after gamma irradiation. Discoloration of silicone tubing can also be induced with heat regardless of PVC cap contact. Several extractable species were found in gamma-irradiated silicone tubing, and the origin of these extractable species is believed to be from the gamma irradiated assembly/packaging material rather than the tubing itself. The extractable species were comparable between the discolored and clear tubing. Furthermore, heat treatment of silicone tubing was effective at reducing these organic extractable species. Neither the extractable species nor discolored tubing has been shown to cause protein particles.

Inconsistencies (from assembly to assembly) in the formation of these visible protein particles pose a challenge for further investigation into the mechanism. Meanwhile, a potential mitigation would be to incorporate a filter close to the filling nozzle into the SU assembly by SU manufacturer. Since these SU assemblies are used for filling DP, it is crucial that manufacturers produce products (may include non-fluid contact material) that are essentially free of extractables, leachables, and particles.