Strategies to deal with challenges of developing high-concentration subcutaneous (SC) formulations for monoclonal antibodies (mAbs)

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The major degradation that occurs at high concentrations of proteins and monoclonal antibodies (mAbs) is aggregation and insolubility. Insolubility of a protein at high concentration can manifest itself as formation of particulates or phase separations including formation of gels. In addition to this, as previously discussed, is the increase of viscosity at higher concentrations which pose challenges for administration and manufacturing. All of these phenomena are linked to protein–protein interactions (PPI) that increase at higher concentration because of the closer proximity of the protein. The role of PPI and impact on properties such as viscosity will be discussed in more detail in the next chapter. Here we will discuss strategies that can be used to mitigate the challenges, in particular, the issue of the impact of viscosity on pharmaceutical development of mAbs.

Using existing manufacturing technologies through redesign of equipment or modification of process variables to produce high-concentration formulations

The most common process unit operation for concentration of proteins and mAbs is tangential flow filtration (TFF). As previously discussed, increases in viscosity and also decreases in diffusion could result in sufficient backpressure, which decreases the efficiency of the process because of exceeding the capacity of the pumps. In addition, interactions with the TFF membranes could result in unfolding of the proteins leading to insolubility issues. Recovery of the concentrated protein from the TFF system may also be problematic because of the higher viscosity, which decreases flow and results in loss of the concentrated drug product (DP). The performance and recovery from TFF systems has been reviewed and involves the design of the TFF properties such as hold-up volumes and tank-working volumes, as well as operational parameters such as system pressure and pump flow rates, which are limited by the viscosity of the solution (Rao, Gefroh, & Kaltenbrunner, 2012). Essentially, the TFF process involves four steps. In the first step, the formulated DS is concentrated to an intermediate concentration lower than the final target, and in the second step, it is diafiltered into the formulation buffer system. In the third step, the solution is concentrated to a level beyond the final targeted concentration. The overconcentration is required since there is a considerable volume of final DP held in piping outside the TFF processing tank, which is often recovered with a formulation buffer flush in the final step resulting in

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