The other methods of particle generation are not any easier to scale-up (27), especially when peptides or proteins are the target molecule. Seemingly sound lab or pilot scale procedures can produce undesirable outcomes at larger scale. Therefore, steps must be taken to ensure that particle generation and size reduction operations are accomplished without affecting the properties of the molecule or reproducibility of the process. Milling operations must be conducted aseptically because no practical means of resterilization is feasible if sterility is compromised. Nonaqueous (oil) vehicles do require special consideration if they are to be sterilized by filtration as filter composition, pore size, and flow rates can impact capture efficiency. Finally, an appropriate strategy needs to be devised for aseptically combining the particles and vehicle.

Following each successive scale-up, it is important to consider comparability[1] of the product properties relative to known characteristics at the previous scale. Expanded physicochemical evaluation beyond routine testing will need to be employed to ensure, for example, that molecular integrity, particle morphology, suspension/sedimentation aspects, dissolution profile, and stability performance (including accelerated and stress conditions) are comparable between scales. Depending upon the stage of clinical development or whether the product is already licensed, it may be necessary to also include nonclinical and/or clinical studies to evaluate in vivo pharmacological performance. Comparability assessments should be considered for other types of changes to the process, such as introducing new raw materials, parameter modifications, or transfer of the process to a different manufacturing facility due to the potential to influence properties of the suspension.

Filling

Suspension homogeneity must be maintained throughout the filling operation to ensure content uniformity in the finished units. Continuous mixing and recirculation are typically conducted to keep particles homogeneously dispersed. The specific type of agitation required is highly dependent on the sedimentation properties of the particles and nature of the vehicle. Careful examination of parameters, such as mixer configuration, mixing/recirculation speed and duration, is necessary to determine optimal conditions. Computational modeling approaches may be useful for defining agitation parameters necessary to achieve optimal particle dispersion. The issues associated with mixing peptide and protein suspensions have already by elaborated. While the concerns are similar for recirculation, there are additional considerations. The recirculation operation involves pumping the suspension through tubing and the impact of this agitation on molecular structure and/or particle integrity needs to be assessed. Product interactions with contact surfaces of equipment used for recirculation should be additionally explored since the duration of filling may last several hours. The potential for leachables from recirculation line tubing also exists raising the same concerns described earlier for the container–closure. One final consideration for suspension filling involves line stoppages. If this situation does occur, stopping the agitation may be advisable in order to minimize exposure of the product to these physical stress conditions. Sufficient time must be allowed upon restart to ensure homogeneity and some population of the filled units will likely be discarded once filling commences to ensure uniformity has been reestablished.

Since some form of agitation is necessary to properly fill a suspension product, a balance must be achieved so that suspension homogeneity is accomplished without impacting the molecule or the particles. One approach to overcome the filling issues associated with suspensions involves particle formation in individual product containers. In this case, fixed volumes of two solutions may be combined together in the vial initiating particle formation. This filling strategy is limited to suspension products where particle formation in aqueous vehicle is feasible. Furthermore, since a commercial batch size could conceivably yield in excess of ten thousands individual units, a thorough understanding of the particle formation process and the influence of associated parameters is essential. Validation of the process must demonstrate that consistency of suspension properties is achieved for each individual unit.

[1] For further details concerning the concept of comparability, consult the following reference: Comparability of biotechnological/biological products subject to changes in their manufacturing process. International Conference on Harmonisation, Q5E, June 2005. This guidance document is available at www.ich.org.