or tissues derived from animals or plants. It is expected that the expression construct for a proposed product will encode the same primary amino acid sequence as its reference product. However, minor modifications, such as N- or C-terminal truncations (e.g., the heterogeneity of C-terminal lysine of a mAb) that are not expected to change the product performance, may be justified and should be explained by the sponsor. Possible differences between the chosen expression system (i.e., the host cell and the expression construct) of the proposed product and that of the reference product should be carefully considered because the type of expression system will affect the types of process- and product-related substances, impurities, and contaminants (including potential adventitious agents) that may be present in the protein product. For example, the expression system can have a significant effect on the types and the extent of translational modifications and PTMs that are imparted to the proposed product, which may introduce additional uncertainty into the demonstration that the proposed product is highly similar to the reference product.

Minimizing the differences between the proposed and reference expression systems to the extent possible can enhance the likelihood of producing an extremely similar protein product. The use of different expression systems will be evaluated on a case-by-case basis.

3.7.2 Manufacturing process

A comprehensive understanding of all the steps in the manufacturing process for the proposed product should be established during product development. Characterization tests, process controls, and specifications that will emerge from information gained during the process development must be specific for the proposed product and the manufacturing process. The use of enhanced approaches in manufacturing is described in guidances for industry such as ICH Q8(R2), ICH Q9, ICH Q10, and ICH Q11. A type II Drug Master File (DMF) may, however, be used to support an IND for a biosimilar product. Assurance of product quality should be provided for each lot of material produced by the DMF holder. Procedures should also be in place to ensure that the IND sponsor is notified by the DMF holder of significant changes to the DMF potentially affecting product quality. The sponsor is expected to provide notification to the Agency of any relevant change in the IND in order to initiate a reevaluation of the DMF.

A sponsor considering manufacturing changes after completing the initial analytical similarity assessment or after completing clinical studies intended to support a 351(k) application will need to demonstrate comparability between the pre- and the postchange proposed product and may need to conduct additional analytical studies. The nature and the extent of the changes may determine the magnitude of these additional similarity studies. The analytical similarity studies should include