On the whole, there is no single stability-indicating assay or parameter that profiles the stability characteristics of a biotechnological/biological product. Consequently, the manufacturer should propose a stability-indicating profile that provides assurance that changes in the identity, purity, and potency of the product will be detected.

At the time of submission, applicants should have validated the methods that comprise the stability-indicating profile, and the data should be available for review. The determination of tests that should be included will be product-specific. The items emphasized in the following subsections are not intended to be all-inclusive but represent product characteristics that should typically be documented to demonstrate product stability adequately.

For the purpose of stability testing of the products described in this guideline, purity is a relative term. Because of the effect of glycosylation, deamidation, or other heterogeneities, the absolute purity of a biotechnological/biological product is extremely difficult to determine. Thus, the purity of a biotechnological/biological product should be typically assessed by more than one method, and the purity value derived is method dependent. For the purpose of stability testing, tests for purity should focus on the methods for the determination of degradation products.

The degree of purity, as well as the individual and total amounts of degradation products of the biotechnological/biological product entered into the stability studies, should be reported and documented, whenever possible. Limits of acceptable degradation should be derived from the analytical profiles of batches of the DS and DP used in the preclinical and clinical studies.

The use of relevant physicochemical, biochemical, and immunochemical analytical methodologies should permit a comprehensive characterization of the DS and/or DP (e.g., molecular size, charge, and hydrophobicity) and the accurate detection of degradation changes that may result from deamidation, oxidation, sulfoxidation, aggregation, or fragmentation during storage. As examples, methods that may contribute to this include electrophoresis (SDS09Page, immunoelectrophoresis, Western blot, and IEF), high-resolution chromatography (e.g., RP chromatography, gel filtration, IEX, and affinity chromatography), and peptide mapping.

Wherever significant qualitative or quantitative changes indicative of degradation product formation are detected during long-term, accelerated, and/or stress stability studies, consideration should be given to potential hazards and the need for the characterization and quantification of degradation products within the long-term stability program. Acceptable limits should be proposed and justified, taking into account the levels observed in material used in preclinical and clinical studies.

For substances that cannot be properly characterized or products for which an exact analysis of the purity cannot be determined through routine analytical methods, the applicant should propose and justify alternative testing procedures.

9.9.5 Forced Degradation Studies

Stress testing studies are conducted to challenge the specificity of stability-indicating and impurity-monitoring methods as part of the validation protocol. The current regulatory guidances governing forced degradation studies of biological pharmaceuticals are extremely general. They itemize broad principles and approaches with few practical instructions. There is no single document that