employed in stability testing should detect low concentrations of aggregates. This is generally tested by providing stress conditions in the downstream processing to study if any unusual decomposition products are formed; a placebo is used as control. Potential degradation pathways are extensively researched, and methods for their detection are well established. A number of comprehensive reviews on this topic are available in the literature.

The proposed stability-indicating methodologies should provide assurance that changes in the identity, purity, and potency of the product will be detected. The selection of tests is product-specific. Stability-indicating methods will characterize potency, purity, and biological activity. As examples, stability-indicating methods may include electrophoresis (SDS-PAGE, immunoelectrophoresis, Western blot, and IEF), high-resolution chromatography (e.g., RP chromatography, SEC, gel filtration, IEX, and affinity chromatography), and peptide mapping.

The selected set of methods must be able to detect, separate, and quantify all observed degradation products; however, it is recognized that the identification and characterization of the appropriate variants may require the use of additional analytical methodologies. New analytical technologies and modifications of the existing technologies are continuously being developed and should be utilized when appropriate. The list of assays challenged by stressed samples should include analytical methods employed in the stability program and those monitoring impurities.

9.9.6 Specifications

Specifications are one part of a total control strategy designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, on which many of the specifications are based; adherence to GMPs; a validated manufacturing process; raw materials testing; in-process testing; stability testing; and so on. Specifications are chosen to confirm the quality of the DS and DP rather than establishing full characterization and should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

Characterization of a biotechnological or biological product (which includes the determination of physicochemical properties, biological activity, immunochemical properties, purity, and impurities) by appropriate techniques is necessary to allow relevant specifications to be established. Acceptance criteria should be established and justified based on the data obtained from lots used in preclinical and/or clinical studies, data from lots used for the demonstration of manufacturing consistency, data from stability studies, and relevant development data.

Extensive characterization is performed in the development phase and, where necessary, following significant process changes. At the time of submission, the product should have been compared with an appropriate reference standard, if available. When feasible and relevant, it should also be compared with its natural counterpart. Also, at the time of submission, the manufacturer should have established appropriately characterized in-house reference materials, which will serve for the biological and physicochemical testing of production lots. New analytical technology and modifications to the existing technology are continually being developed and will be utilized when appropriate.