mediate their effect by the transcription and/or translation of the transferred genetic material and/or by integration into the host genome. Cells may be modified in these ways ex vivo for subsequent administration to the recipient or altered in vivo by gene therapy products administered directly to the recipient.

- Vaccines (products intended to induce or increase an antigen-specific immune response for prophylactic or therapeutic immunization, regardless of the composition or method of manufacture).
- Allergenic extracts used for the diagnosis and treatment of allergic diseases and allergen patch tests.
- Antitoxins, antivenins, and venoms.
- Blood, blood components, plasma-derived products (e.g., albumin, Igs, clotting factors, fibrin sealants, and proteinase inhibitors), including recombinant and transgenic versions of plasma derivatives (e.g., clotting factors), blood substitutes, plasma volume expanders, human, or animal polyclonal antibody preparations, including radiolabeled or conjugated forms, and certain fibrinolytics, such as plasma-derived plasmin and red cell reagents.

Significant developments over the past couple of decades have resulted in the development of a new class of biopharmaceutical products based on recombinant DNA technology that has placed a greater burden on the developer to provide characterization protocols that take into account modifications induced by the recombinant techniques. Generally, the analytical precision for these molecules has not been as sophisticated as that available for small molecules; a few thousand Daltons seemed to be the limit of analytical accuracy; the characterization method essentially require biological methods that are by nature more variable. However, recent developments in both in vivo and in vitro studies needed to ensure comparable safety and efficacy; the powerful techniques, such as the high-resolution tandem mass spectrometry, circular dichroism, and chromatographic media, make it possible to provide complete covalent structure for proteins over 100,000 Da, with less than one Dalton change in proteins routinely detectable. The newer sensitive methods now detect differences in the HOS, and for all practical purposes, it is reasonable to conclude that the historic differences between characterization specifications have been removed.

9.8 Preformulation Studies

The unique nature of characteristics of biological products requires early integration of scientific activity bringing onboard protein biochemists, purification scientists, quality control and regulatory affairs personnel, clinical investigators, manufacturing technicians, marketing specialists, and managers.

The diversity of preformulation studies required to characterize biological drugs requires the application of a comprehensive array of multiple sensitive and selective analytical methods to several batches. This requires the use of orthogonal methods to study virtually every observable property of a protein, including covalent structure, conformation, pI, aggregation, charge, mass, fragmentation, surface structure, hydrophobicity, spectrophotometric, magnetic resonance, fluorescence, light scattering, sedimentation, electrophoretic properties, charge, immunological properties,