drugs are administered at the microgram level, many MAbs are given in much larger quantities (hundreds of milligrams per dose) and are normally delivered intravenously. The drive to reduce healthcare costs has created a need to administer MAb therapeutics more conveniently, at home, subcutaneously. Thus, MAbs must be available at high concentrations (~200 mg/mL) in the vial. At these high concentrations, MAb-containing solutions are viscous, making them difficult to administer conveniently. Hence, a preformulation activity that needs to be considered is a concentration study investigating the solubility behavior, the effect of concentration on viscosity, and the increased potential for aggregation. These studies have the potential to strongly influence the target product profile and the design of the clinical trial. Similarly, such questions as to whether a drug is going to be administered in a freeze-dried form or liquid form focus the studies accordingly. These considerations are mostly determined by stability considerations, as freeze-drying imparts greater stability; however, some recent studies suggest that the reconstitution process can alter the 3D structure of proteins, making them more immunogenic.

Preformulation begins with thorough characterization of proteins, including their pharmacokinetics and physicochemical characterization. Ideally, this information should be in hand at the beginning of the product development program, but this is unrealistic, as product characterization is an evolving process that involves contributions at different stages of the product life cycle.

### 9.8.1 Stability

The most difficult aspect of biopharmaceutical stabilization is the ease with which these products begin to show aggregation, something that is often difficult to predict. As a result, evaluation of biopharmaceutical products focuses on both physical and chemical stability studies that investigate temperature dependencies to convert in vivo to native forms (if it has denatured). Bioassays study protein activity, identity, and critical pathways. Chemical degradation changes the primary structure of a protein. Bond cleavage will create an entirely new molecule. Such chemical degradation is usually preceded by a causal physical process, typically unfolding, which makes available residues that are usually inaccessible for chemical reactions with their environment. Physical degradation changes only the HOS (secondary, tertiary, and quaternary) of the polypeptide, not necessarily creating a brand-new molecule. Such degradation includes aggregation, adsorption, unfolding, and precipitation.

Because proteins and peptides are such large molecules and exist to interact with their environment, they are somewhat fragile. They must be protected from denaturation and degradation until they can be delivered to their site of action in a patient's body.

The biopharmaceutical development process does not allow enough time to confirm stability requirements for a final formulation (which could take two years) before the company is otherwise ready to apply to market the product. Initial indications should be developed during clinical studies, so formulators must begin with 3-, 6-, and 9-month tests of their molecule's structure and innate stability by using various analytical methods. "Accelerated" stability tests subject products to various stresses: a range of pH values, heat, light, freezing and thawing conditions, additives, and surface materials and interfaces. The test for agitation-induced denaturation is performed by swirling (creating a vortex inside the vials), rotating vials at elevated temperatures, and testing the surface tension of the liquid formulation.