Because the herbal drug or the herbal drug preparation in its entirety is regarded as the active substance, a mere determination of the stability of the constituents with known therapeutic activity will not suffice. It must also be shown, as far as possible, for example, by means of appropriate fingerprint chromatograms, that other substances present in the herbal drug or in the herbal drug preparation are likewise stable and that their proportional content remains constant.

If an herbal medicinal product contains several herbal drugs or preparations of several herbal drugs and if it is not possible to determine the stability of each active substance, the stability of the medicinal product should be determined by appropriate fingerprint chromatograms, appropriate overall methods of assay, and physical and sensory tests or by other appropriate tests. The appropriateness of the tests should be justified by the applicant.

In the case of an herbal medicinal product containing a herbal drug or herbal drug preparation with constituents of known therapeutic activity, the variation in content during the proposed shelf life should not exceed ±5% of the initial assay value, unless justified. In the case of a herbal medicinal product containing a herbal drug or herbal drug preparation, where constituents with known therapeutic activity are unknown, a variation in content during the proposed shelf life of ±10% of the initial assay value can be accepted, if justified by the applicant. These criteria also apply to the stability testing of active substances in a similar manner.

3.3.3 Large-Molecule Drugs

A biopharmaceutical drug can go into development before anyone knows much about how it works. The protein may be identified through genomics or proteomics activities or through more traditional medical research. It may initially be associated with a particular disease process or a certain metabolic event. In any case, its mechanism of action—as well as many of its structural characteristics and biochemical properties—may be unknown. One of the more challenging aspects of developing protein pharmaceuticals is dealing with and overcoming the inherent physical and chemical instabilities of proteins. This inherent instability has the potential to alter the state of the protein from the desired (native) form to an undesirable form (upon storage), compromising patient safety and drug efficacy. Marketing concerns come up earlier in the development of protein drugs. Route of administration is determined by the target product profile and if the product will treat a chronic or acute disorder, if it will need specific targeting—a broad or narrow therapeutic window—or if it will be administered at home or in the clinic or hospital. For example, marketing considerations arise early in product development for monoclonal antibodies (MAbs). Typically, MAbs are needed at high doses (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.