Stress studies may be useful in determining whether accidental exposures to conditions other than normal ranges (e.g., during transportation) are deleterious to the product and also for evaluating which specific test parameters may be the best indicators of product stability.

9.9.5.1 Stress Testing

This involves the establishment of a stability-indicating analytical procedure that will detect significant changes in the quality of DS at Phase II stage of IND. Stress studies on DS and DP should be completed during Phase III, and significant impurities should be identified, qualified, and quantified. Starting forced degradation experiments before Phase II is highly encouraged and should be conducted on DS, with multiple aims: to provide timely recommendations for improvements in the manufacturing process; to ensure proper selection of stability-indicating analytical techniques; and to assure sufficient time for the identification of degradation product, elucidation of degradation pathways, and optimization of stress conditions.

Every change in stability-indicating analytical methods, manufacturing processes, or formulation requires revalidation of analytical methods; therefore, full validation commences only after the manufacturing process is finalized, formulations are established, and test procedures are developed and qualified. However, method validation must be completed before a formal long-term stability study begins. These limitations impose time constraints on all method-validation activities, including stressed sample development and testing. Consequently, all preliminary work on optimization of stress conditions must be completed at the earlier stages, even though results of forced degradation studies are not required to be reported until Phase III stage of IND application.

The question of how much degradation is sufficient to meet the objectives of stress studies is widely discussed, especially with respect to conventional therapeutics. A degradation level of 10%–15% is considered adequate for validation of a chromatographic purity assay. Chromatographic methods for product-related impurities (including degradants) should be validated by spiking experiments within the range of 0%–20% if the expected range of impurities is 0%–10%. It is also suggested that DS spiked with a mixture of known degradation products can be used to challenge the methods employed for monitoring stability of DP. The apparent consensus among pharmaceutical scientists is that samples degraded ~10% are optimal for use in the validation of analytical method. These considerations apply to small organic pharmaceuticals for which stability is dictated by the typical pharmaceutical limit of 90% of label claim.

No such limits for physicochemical changes, losses of activity, or degradation during shelf life have been established for individual types or groups of biological products. In general, international and national regulations for biological products provide little guidance with respect to stability-related issues. These issues should be considered on a case-by-case basis.

As a group, biological products form a wide variety of product-related degradants under stress conditions. In cases with multiple degradation pathways, it appears to be beneficial to develop multiple product-related variants to challenge the specificity of analytical methods, even when some of the degradants may be present at concentrations that exceed 10%. This is done when accelerated stability studies do not provide clear indication of the degradation pathways. When a stress factor generates only one degradation product, for example, higher-MW noncovalent aggregates, 10%–15%