9.9.14 Justification of Specifications

The setting of specifications for DS and DP is part of an overall control strategy, which includes control of raw materials and excipients, in-process testing, process evaluation or validation, adherence to GMPs, stability testing, and testing for the consistency of lots. When combined in total, these elements provide assurance that the appropriate quality of the product will be maintained. As specifications are chosen to confirm the quality rather than to characterize the product, the manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes. The following points should be taken into consideration when establishing scientifically justifiable specifications:

- Specifications are linked to a manufacturing process.
- Specifications should be based on data obtained from lots used to demonstrate manufacturing consistency. Linking specifications to a manufacturing process is important, especially for product-related substances, product-related impurities, and process-related impurities. Process changes and degradation products produced during storage may result in heterogeneity patterns that differ from those observed in the material used during the preclinical and clinical development. The significance of these alterations should be evaluated.
- Specifications should account for the stability of DS and DP.
- Degradation of DS and DP, which may occur during storage, should be considered when establishing specifications. Owing to the inherent complexity of these products, there is no single stability-indicating assay or parameter that profiles the stability characteristics. Consequently, the manufacturer should propose a stability-indicating profile. The result of this stability-indicating profile will then provide assurance that changes in the quality of the product will be detected. The determination of the tests that should be included will be product-specific. The manufacturer is referred to the ICH guidance *Q5C Stability Testing of Biotechnological/Biological Products*.
- Specifications are linked to preclinical and clinical studies.
- Specifications should be based on the data obtained for lots used in preclinical and clinical studies. The quality of the material made at the commercial scale should be representative of the lots used in the preclinical and clinical studies.
- Specifications are linked to analytical procedures.

Critical quality attributes may include items such as potency, the nature and quantity of product-related substances, product-related impurities, and process-related impurities. Such attributes can be assessed by multiple analytical procedures, each yielding different results. In the course of product development, it is not unusual for the analytical technology to evolve in parallel with the product. Therefore, it is important to confirm that the data generated during development correlate with those generated at the time the marketing application is filed.