of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products should be considered.

9.9.10 Quantity

Quantity, usually measured as protein content, is critical for a biotechnological/biological product and should be determined using an appropriate assay, usually physicochemical in nature. In some cases, it may be demonstrated that the quantity values obtained may be directly related to those found using the biological assay. When this correlation exists, it may be appropriate to use the measurement of quantity rather than the measurement of biological activity in manufacturing processes, such as filling.

9.9.11 Analytical Considerations

9.9.11.1 Reference Standards and Reference Materials

For drug applications of new molecular entities, it is unlikely that an international or national standard will be available. At the time of submission, the manufacturer should have established an appropriately characterized in-house primary reference material, prepared from lot(s) representative of production and clinical materials. In-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material. Where an international or national standard is available and appropriate, reference materials should be calibrated against it. While it is desirable to use the same reference material for both biological assays and physicochemical testing, in some cases, a separate reference material may be necessary. Also, distinct reference materials for product-related substances, product-related impurities, and process-related impurities may need to be established. When appropriate, a description of the manufacture and/or purification of reference materials should be included in the application. Documentation of the characterization, storage conditions, and formulation supportive of reference material(s) stability should also be provided.

9.9.11.2 Validation of Analytical Procedures

At the time at which the application is submitted to the regulatory authorities, applicants should have validated the analytical procedures used in the specifications in accordance with the ICH Guidances *Q2A Validation of Analytical Procedures: Definitions and Terminology* and *Q2B Validation of Analytical Procedures: Methodology*, except where there are specific issues for unique tests used for analyzing biotechnological and biological products.

9.9.12 Process Controls

Adequate design of a process and knowledge of its capability are parts of the strategy used to develop a manufacturing process that is controlled and reproducible, yielding a DS or DP that meets the specifications. In this respect, limits are justified based on