Test method validation is needed to conduct clinical trials. Specifications should start off wide for Phase I and narrow to tighter values in the license application. Relaxing established specifications is very difficult.

9.9.3.8 Software Validation

Software validation operates under the principle that quality should not be diminished if a manual process is replaced with an automated process. Software must be developed and tested under a quality system with defined user requirements, change-control procedures, provisions for authorization of operators for data entry and data checking, data archiving, software backup, provisions for system crashing, and procedures for monitoring and correcting software problems. 21 CFR 11 defines requirements for maintaining the integrity of data and software and handling electronic signatures for traceability.

9.9.3.9 Cleaning Validation

Cleaning validation demonstrates the ability of cleaning procedures to permit the reuse of processing components and equipment, without a concomitant deterioration of product quality. Batch-to-batch carryover is of concern in multiuse plants making more than one product.

Consistency of product quality is demonstrated by showing operating consistency and product quality from batch to batch, processing with only buffer (blank runs) with assays for contaminants, examination of cleaned surfaces and materials, and extended scale-down clearance studies on reused materials. Disposable processing components that eliminate the need for cleaning validation are increasingly used at a small scale.

9.9.3.10 Expression System Characterization

This is performed before Phase I studies in humans to ensure safety. Concerns include the presence of contaminating organisms, tumorigenic cells, proteins, nucleic acids, retroviruses, or other pathogens. Taking tissue culture as an example, characterization includes the source, raw materials used, selection methods, number of generations, transfection or fusion methods used, procedures for establishing working cell banks, facilities, identity, homogeneity, absence of contaminating pathogens, tumorigenicity, and stability.

9.9.4 Stability Considerations

Commercial viability of recombinant production processes depends on the final product yield. This is a particularly more significant issue, as biogeneric manufacturers bring out their line of products that will be sold at a lower price than the innovator's products; the issue of yield becomes more important now. A primary cause of poor yield is neither the quality of the gene construct nor the nature of the molecule but the degradation of the product during the manufacturing process. Protein degradation therefore becomes a key factor that must be thoroughly understood, and steps must