specification, extractables' and leachables' characterization, and clearance studies. Such work depends on validated assays and representative scale-down models.

Process development normally involves identifying critical variables, defining setpoints for each unit operation, and establishing operating ranges (deviations from the setpoint). Maximum operating range (MOR) limits are typically set during Phase II or III. If they are exceeded, an investigation is necessary to determine if product quality remains acceptable.

Normal operating range (NOR) limits are determined by run-to-run reproducibility with scale-down models and trending with control charts at production scale. The NOR limits lie within the MOR limits, which must allow for normal variability while maintaining acceptable operation.

9.9.3.6 Facility and Equipment Validation

Facility and equipment validation is normally divided into design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). Equipment validation begins with pilot production of clinical materials for Phase II.

The DQ provides documented evidence that the proposed design of the facilities, equipment, and systems is suitable for the intended purpose. The DQ must compare the design to a set of well-defined user requirements relating to product safety, identity, strength, purity, and quality.

The IQ provides documented evidence that the system is assembled, installed, plumbed, and wired according to the user's design specifications, vendor recommendations, and appropriate codes and standards. Vendors typically provide much of the hardware documentation.

The OQ provides documented evidence that the system performs as expected throughout its intended operating ranges, including all the system's different functions and all its components (hardware, monitoring instruments, controls, alarms, and recorders). Elements of the OQ testing and documentation may be part of the factory acceptance test at the vendor's site. Integration with plant utilities and component installation must be verified at the factory. Hardware cleanliness must also be assessed after cleaning.

The PQ is documented by processing actual feedstock by trained operators by using buffers and utilities at the factory. Full-scale process validation includes testing the consistency of batch production.

9.9.3.7 Analytical Methods

Several methods are used to measure the product characteristics important for therapeutic safety and efficacy during preclinical and early Phase I studies. Additional tests are developed for final product release and in-process sampling of the final manufacturing process. These measure characteristics such as molecular identity, purity, potency, and safety. The number of tests should be sufficient to show manufacturing consistency and the impact of manufacturing changes. Once a test is made a formal part of the manufacturing process, it is almost impossible to remove. Test methods are evaluated for different attributes such as accuracy, precision, range, selectivity, recovery, calibration (detection and quantitation limits), assay sampling, robustness, and stability.