critical information gained from the entire process, spanning the period from early development through commercial-scale production.

For certain impurities, testing of either the DS or the DP may not be necessary and may not need to be included in the specifications if efficient control or removal of acceptable levels is demonstrated by suitable studies. This testing can include verification at the commercial scale, in accordance with regional regulations. It is recognized that only limited data may be available at the time of submission of an application. This concept may, therefore, sometimes be implemented after marketing authorization, in accordance with regional regulations.

In-process tests are performed at critical decision-making steps and at other steps where data serve to confirm consistency of the process during the production of either the DS or the DP. The results of in-process testing may be recorded as action limits or as acceptance criteria. Performing such testing may eliminate the need for testing the DS or DP. In-process testing for adventitious agents at the end of cell culture is an example of testing for which acceptance criteria should be established.

The use of internal action limits by the manufacturer to assess the consistency of the process at less critical steps is also important. Data obtained during development and validation runs should provide the basis for provisional action limits to be set for the manufacturing process. These limits, which are the responsibility of the manufacturer, may be used to initiate investigation or further action. They should be further refined as additional manufacturing experience, and data should be obtained after product approval.

The quality of the raw materials used in the production of the DS (or DP) should meet the standards appropriate for their intended use. Biological raw materials or reagents may require careful evaluation to establish the presence or absence of deleterious endogenous or adventitious agents. Procedures that make the use of affinity chromatography (e.g., employing MAbs) should be accompanied by appropriate measures to ensure that such process-related impurities or potential contaminants arising from their production and use do not compromise the quality and safety of the DS or DP. Appropriate information pertaining to the antibody should be made available.

The quality of the excipients used in the DP formulation (and in some cases, the DS), as well as the container/closure systems, should meet pharmacopoeial standards, where available and appropriate. Otherwise, suitable acceptance criteria should be established for the nonpharmacopoeial excipients.

9.9.13 Release Limits versus Shelf-Life Limits

The concept of release limits versus shelf-life limits may be applied where justified. This concept pertains to the establishment of limits that are tighter for the release than for the shelf life of the DS or DP. Examples where this may be applicable include potency and degradation products. In some regions, the concept of release limits may only be applicable to in-house limits and not to the regulatory shelf-life limits.

Appropriate statistical analysis should be applied, when necessary, to the quantitative data reported. The methods of analysis, including justification and rationale, should be described fully. These descriptions should be sufficiently clear to permit independent calculation of the results presented.