The generic drug scandal of the late 1980s propelled the enhancement of cGMP compliance enforcement. Until the scandal, GMP compliance inspections occurred on a routine basis, sometimes two or more years after a new drug application (NDA) or abbreviated new drug application (ANDA) was submitted and approved by the FDA. During and after the scandal, starting in 1990, the FDA introduced "preapproval GMP inspections" where local and/or regional GMP compliance inspections occur soon after the regulatory dossier has been submitted. Prior to approving the application FDA headquarters would need to receive a recommendation from the GMP compliance inspectors. Therefore, even today cGMP compliance now impacts approvability of NDAs and ANDAs (shown schematically in Fig 5-2, p. 51).

Preapproval inspections required the manufacturer to accelerate final product/process validation studies. Prior to preapproval inspections, manufacturers would submit process information that had not yet been done. Indeed, often manufacturers would wait for FDA approval of a NDA before finalizing equipment selection/purchase or even building the facility to manufacture the commercial product. Preapproval inspections required manufacturers to finalize the manufacturing process with evidence of validation of the process at commercial scale prior to submitting the NDA.

During the first few years of preapproval GMP inspections, roughly 40% of NDAs and ANDAs were withheld approval because of GMP compliance problems uncovered at the manufacturing facility and/or testing laboratory. The major reasons for failing preapproval inspections in the early 1990s were in order of frequency:

1. Facility noncompliance
2. Laboratory noncompliance
3. Any discrepancy suggesting fraud or deception
4. Lack of data supporting process control
5. Clinical batch analytical and performance data do not correlate to data from production batches
6. Lack of acceptable validation controls
7. Excessive number of cGMP problems.

Generally, the most common problem found during GMP inspections is the failure to follow written standard operating procedures (SOPs). This has been true since cGMP regulations became enforced and backed by law. Another common GMP noncompliance problem is the failure to follow good documentation practices (see Chapter 26). Table 25-3 lists a wide variety of specific 483 observations found during GMP compliance inspections of sterile manufacturing drug plants.

The GMP inspection process can be relatively simple if the FDA inspection team finds no problems with GMP compliance during the inspection. However, if problems are found, depending on their severity and/or frequency, the following sequence of regulatory activity can occur:

1. Inspections are usually preapproval or annual or biannual visits.
2. Inspections can also be prelicensing inspections (for biologics), follow-up inspections from previous inspection or stimulated by some problem, e.g. complaint and recall.
3. At the conclusion of an FDA inspection, the inspection team communicates its observations to the inspected company via Form FDA-483 (or simply, "483").
4. Upon returning to the FDA District Office, the inspection team writes an Establishment Inspection Report (EIR) that elaborates and expands on the inspection observations and links the observations to the evidence collected to support them. The EIR is reviewed, and if the conditions it describes are serious enough in the minds of the reviewing officials, a Warning Letter may follow.
5. A Warning Letter may also be issued if the FDA is not satisfied with the timing or content of the firm's response(s) to the 483 observations.
6. A Warning Letter differs from a 483 in several important respects. A 483 represents the observations of the inspection team (or lone investigator, if such is the case). A Warning Letter indicates that higher level FDA officials have reviewed the inspection findings and have concluded that the findings warrant further formal notification to the inspected company that FDA believes serious violations may exist.