Table 25-3 Examples of Specific 483 Observations During cGMP Compliance Inspections of Sterile Drug Manufacturing Plants (*Continued*)

- Failure to replace faulty HEPA filters
- No air flow pattern testing in aseptic areas
- Lack of classified environments after vial stoppering
- No justification of selected surfaces for EM
- Smoke studies do not fully demonstrate air flow movement away from work surfaces during personnel activities
- No attempt made to determine correlation between a product defect (visible precipitate) and consumer complaints
- Inadequate investigations/response to other product complaints; no root cause determined
- Failure to follow timeframes in SOPs for completing investigations
- Particle monitoring locations not very close to filling zones and exposed product
- No preventive maintenance schedules for stability chambers, freezers, etc.
- Personnel with factory scrubs and dedicated shoes allowed access to common personnel hallways where nongowned personnel are also located
- Inadequate investigations of OOS results

Abbreviations: WFI, water for injection; EM, environmental monitoring; OOS, out-of-specification.

7. A Warning Letter has a twofold purpose: (*i*) to stimulate voluntary corrective action and (*ii*) to establish a background of prior warning should further regulatory action by FDA be needed at a later date.
8. Warning letters should be issued only for violations of "regulatory significance." The threshold for determination of what constitutes "regulatory significance" is that failure to adequately and promptly achieve correction to the warning letter may be expected to result in enforcement action . . . the warning letter would be appropriate to document prior warning if adequate corrections are not made and subsequent enforcement action is warranted, that is, injunction or prosecution.
9. Both the 483 and the Warning Letter are serious documents that warrant a prompt and thoughtful reply. Companies often tend to rush replies at the expense of careful consideration of the issues. Many companies believe that a rapid response to a 483 will prevent a Warning Letter. In certain cases this may be true, but a rapid 483 reply is no guarantee that a Warning Letter will not follow. A poorly written 483 response, on the other hand, may very well increase the likelihood of a subsequent Warning Letter.

Hundreds of Warning Letters were issued during the first few years (1990–1994) after initiating this documentation as a regulatory enforcement activity. These years also witnessed a huge number of product recalls, seizures, injunctions, and prosecutions as the FDA purged the industry of unscrupulous pharmaceutical companies and individuals. Issuance of 483s and Warning Letters are still common today, but not as bad as many years ago.

The FDA also began an enforcement activity called "Consent Decree" for companies that are in so much out of compliance with GMPs that it will take months to years to return to compliance. The FDA issues consent decrees to resolve long-term and significant GMP noncompliance problems with the intent to ensure production and distribution of safe and effective drug products. The consent decree outlines steps that the company must take to become compliant with penalties for failing to meet conditions and schedules. Consent decrees are issued because of recurrent failures:

- To ensure products meet quality standards prior to release
- To conduct adequate lab investigations
- To maintain lab equipment
- To keep adequate records
- To complete validation of products
- Equipment cleanliness
- Insufficient employee training
- Poor QC oversight and practices.