

II. The Agency's Retrospective Review

The agency conducted an internal retrospective review (the review) of CGMP regulations to determine if any existing provisions should be changed, modified, or removed. Based on that review, the agency concluded that there was a continuing need for the CGMP regulations to protect public health and safety. FDA's examination of individual CGMP provisions revealed that most were necessary and effective in addressing the underlying issues and concerns. The review did, however, result in recommended changes in particular CGMP regulations. These changes were intended to provide drug manufacturers with more flexibility and discretion in manufacturing drug products while maintaining the manufacturing control necessary to ensure drug product quality. The proposed changes are discussed below.

Section 211.42(c) requires separate or defined areas for a firm's operation to prevent contamination or a mixup of drug products or their ingredients. Although the agency's review found that, in general, this provision did not, with the exception of areas of aseptic processing or penicillin production, require the construction of physical barriers, FDA recognized that the word "defined" might be subject to differing interpretations. FDA concluded that amending this provision would clarify that, in most cases, manufacturers may exercise their judgment to determine whether separate or defined areas of production and storage are necessary. The agency is currently evaluating the matter of separate or defined areas of production and storage and may, if necessary, issue further clarification in the future.

Several CGMP regulations require that manufacturers take steps to check the accuracy of equipment used in drug production. For example, § 211.68(b) addresses the accuracy of computerized records and data. A number of comments opposed routine checking of the accuracy of input to or output from a previously validated computer on the basis that it was duplicative, redundant, and expensive. FDA reviewed these comments and concluded that, although automated systems may be less prone to error, such systems are not perfect and need to be monitored. Following its review, however, FDA agreed that the degree of monitoring required for computerized systems would differ from that required for manual operations. FDA concluded that this provision of the CGMP regulations should be revised to clarify that the degree and frequency of input/output verification be based on

the complexity and reliability of the computer or related system.

Before its retrospective review of the CGMP regulations, FDA declined to grant investigational drug products an unqualified exemption from all or most of the CGMP requirements. Following the retrospective review, however, FDA concluded that it was not always possible to obtain expiration dates for investigational drug products because relatively little stability data may be available at the beginning of a clinical investigation. FDA concluded that the expiration dating requirement should be eliminated for investigational new drug application (IND) products so long as such products otherwise meet the stability requirements provided in the regulation.

Section 211.170(b) requires that most reserve samples be examined visually at least once a year for evidence of deterioration. Manufacturers must keep reserve samples that are representative of each lot or batch of finished drug product. The reserve sample is to consist of at least twice the quantity necessary for all required tests. Comments responding to the July 14, 1981, notice, as well as other communications subsequently received by the agency, recommended deleting this requirement because of the large cost to firms that produce large numbers of lots (or batches) of a drug product. The comments further asserted that this requirement was redundant given other provisions of the regulations.

FDA declines to eliminate this requirement because suggested alternatives do not provide effective surveillance of all lots of a drug product. The agency believes the yearly inspection is necessary to ensure the quality of the drug product. However, following the retrospective review, FDA concluded that manufacturers could meet their obligations under this regulation in a less burdensome way by conducting an annual visual inspection of reserve samples from a representative number of reserve sample lots. Therefore, FDA is revising the regulation to permit the use of a representative sampling plan for examination of reserve samples.

Section 211.180 provides general requirements for the retention, treatment, and handling of CGMP records and reports. Section 211.180(e) requires the evaluation, at least annually, of the quality standards of each drug to determine the need for changes in drug product specifications. Firms must establish and follow written procedures for these annual evaluations, and § 211.180(e)(1) and (e)(2) requires that several specific items be included

in such written procedures. For example, § 211.180(e)(1) requires these written procedures to provide for "[a] review of every batch, whether approved or rejected, and, where applicable, records associated with the batch."

Following the retrospective review, FDA concluded that some manufacturers, rather than examining representative batch records for each drug product manufactured during the year, construed this provision to require that every batch record was to be reviewed annually and evaluated according to written procedures. Following the retrospective review, FDA decided to clarify § 211.180(e)(1) on this point.

III. Comments on the Proposed Rule

FDA received several comments on the proposed rule. These comments came from pharmaceutical manufacturers, trade associations, and consumers. In general, the comments supported the agency's efforts to remove, where possible, regulatory requirements that could be eliminated without adversely affecting drug product quality. A section-by-section summary of the comments and the agency's response follow.

A. Design and Construction Features

Confusion about the interpretation of § 211.42(c), which requires separate or defined areas for a firm's operation to prevent contamination or mixup, led to the proposed revision of this provision. The proposed revision was intended to clarify that, in many situations, other control systems may be used in lieu of complete physical separation. The proposal would require separate or defined areas to prevent contamination or mixup "as necessary."

1. Comments on proposed § 211.42 generally supported the revision. Three comments, however, recommended that the wording be modified. One comment requested that the revision more explicitly emphasize that the utilization of computer-controlled inventory systems obviates the need for physical separation. Two comments suggested removal of any reference to separate or defined areas.

The agency agrees in part and disagrees in part with these comments. The preamble to the proposed rule noted that § 211.42(c) is intended to ensure that sufficient physical separation exists in manufacturing operations to prevent contamination or mixups, and that the degree of separation is dependent on the type of operation and its proximity to other operations in the plant (56 FR 5671 at