that this provision requires visual examination of reserve samples from representative sample lots or batches of a drug product once a year for evidence of deterioration unless such examination would affect the integrity of the reserve sample. The representative sample lots or batches would be selected by acceptable statistical procedures.

7. Although most comments agreed with the proposed change, several questioned the value of the annual visual examination requirement given other required procedures and programs such as stability testing, production record reviews, and complaint

investigations.

The agency has carefully considered these comments and has concluded that the requirement for annual visual inspection should be retained. A sufficient number of batches may not be examined during the course of fulfilling the other required procedures and programs, or batches examined may not be representative of annual batch production. As a result, these other procedures and programs cannot replace the annual visual examination, which provides both manufacturers and consumers a greater degree of quality assurance.

8. Three comments requested clarification of the terms "representative" and "acceptable

statistical procedures.'

The agency does not believe that it is necessary or useful to define these terms. The terms have been used in the CGMP regulations for over a decade without apparent confusion due, in part, to a widespread recognition that the meaning of the term "representative" may vary from one product to another as well as with respect to the various manufacturing processes involved in producing a variety of products. In addition, an incomplete definition might fail to encompass the full variety of regulated products and processes, whereas a complete and inclusive definition with regard to currently available products and technology might not easily be adapted to new technology. Similarly, with respect to the term "acceptable statistical procedures," a more detailed definition would not permit adaptation to or evolution with advances in statistical analysis.

9. Another comment suggested that the phrase "acceptable statistical procedures" could be interpreted to require FDA approval. The comment suggested that the term be changed to "appropriate statistical procedures."

As noted above, the agency does not believe that the suggested change is

necessary or useful. The agency emphasizes that the selection of acceptable statistical procedures does not involve prior agency approval. The choice of such procedures should, however, be based on a knowledge of current statistical methodology and include consideration of the application of such methodology to a particular drug product.

E. General Requirements

Section 211.180(e) requires that written records be maintained so that the data contained therein are available at least annually for evaluation of the quality standards for drug products. Proposed § 211.180(e)(1) was intended to correct the misinterpretation that the regulation required the review of every batch record for every drug product produced during the year. The proposed rule revised the language to require at least annually a review of a representative number of batch records.

10. One comment noted that current technology makes it possible to use computer data to evaluate product quality data to detect adverse trends. The comment asserted that such an approach permitted more effective and frequent evaluation of such data.

The agency agrees that technological advances can produce gains in both the accuracy of data evaluation and the speed at which the process can be conducted, and FDA encourages the use of technology that helps safeguard the integrity of the manufacturing process. However, such computerized information must be used as a complement to, and not as a substitute for, human judgment and intervention. Computerized assessments must be monitored by qualified individuals to detect trends that may provide an early indication of changes in drug product specifications or manufacturing or control procedures that merit attention and intervention. Moreover, other factors such as product complaints and recall information may not be included in the computer data.

11. Several comments requested clarification about the types of records subject to the batch review requirement.

The proposed rule was not intended to change the types of records subject to annual review, but instead to allow review of a representative number of batches in lieu of examining all records from every batch. FDA has, therefore, clarified the final rule to require a review of a representative number of batches, whether approved or rejected, and where applicable, records associated with those batches.

The overall intent of § 211.180(e) is to provide manufacturers with reliable

procedures for reviewing the quality standards for each drug product. Thus, FDA advises that, although this final rule does not in all cases require an annual review of every batch record, adopting a procedure to check every batch record would clearly be appropriate if, for example, a representative review of batch records showed an adverse trend in quality.

12. One comment advised that some firms may confuse the requirements with regard to the annual review of representative batches with the requirements for batch review prior to the release of a product under § 211.192.

FDA disagrees with the comment. The final rule amends § 211.180(e), which requires that written records be maintained so that data can be used for evaluating, at least annually, the quality standards of each drug product. Section 211.192, by contrast, specifically requires a quality control unit to review drug product production and control records to determine compliance with written procedures prior to the release of a drug product batch. In brief, § 211.180(e) involves a retrospective overall evaluation of the adequacy of the quality standards for drug products, while § 211.192 involves a contemporaneous evaluation of a drug batch to determine its conformity, at the time of marketing, with current quality standards.

13. One comment suggested allowing a biennial review to permit trend analysis when three or fewer product batches are produced each year.

FDA disagrees with this comment. The agency believes that a 2-year interval between formal review of batches is inadequate. Potential problems with product quality standards could go undetected and thereby delay recognition of a need to revise specifications or manufacturing or control procedures. If a serious error is not detected for a long period, the resulting product could pose a threat to public health and safety. Moreover, a trend analysis may be performed in situations where only a few batches are produced annually by using batches produced in preceding years.

14. One comment strongly opposed the proposed changes, stating that every batch record must be reviewed to detect "drift" or changes in specifications for components, manufacturing processes, or other procedures. The comment asserted that, without reviewing every batch, deleterious changes might be instituted by a firm employee or employees without the full knowledge of their superiors, particularly the firm's research and development group.