5672). The proposed revision was intended to make it clear that the regulation did not necessarily require a separate room or partitioned area. The agency does not, however, intend to disallow the possibility that, in certain instances, it may be necessary to require physical separation to prevent contamination or mixups and, as discussed above, is continuing to review this matter. Sophisticated computer systems may provide more effective inventory control and help reduce mixups, but certain substances, such as penicillin, may pose such a high risk of contamination that a separate or defined area is necessary to ensure the safety of

drug products.

The agency has, therefore, retained the reference to separate or defined areas but has revised the final rule to clarify that other control systems may be used that are capable of preventing contamination and mixups. The agency stated in the preamble to the CGMP regulations published in the Federal **Register** of September 29, 1978 (43 FR 45014 at 45037), and reiterated in the proposed rule (56 FR 5671 at 5672 and 5673), and states again here that this provision is intended to ensure that: 'enough physical separation be employed as is necessary to prevent contamination or mixups. The degree of separation will depend on the type of operation and its proximity to other operations within the plant. The phrase 'separate or defined' is not intended necessarily to mean a separate room or partitioned area, if other controls are adequate to prevent mixups and contamination.

The agency, on its own initiative, has also revised § 211.42 to clarify that the procedures in paragraphs (c)(1) through (c)(10) of that regulation should be protected from contamination or mixups.

## B. Automatic, Mechanical, and Electronic Equipment

Section 211.68(b) deals with controls to be exercised over computer operation, data, and records. The provision requires, in part, that input to and output from a computer system or any related or similar system of formulas or data shall be checked for accuracy. The proposal would add a sentence stating that the degree and frequency of input/output verification from a computer or related system of formulas or other records or data are to be determined by the complexity and reliability of such a computer or related

2. Although all comments supported the proposed change to §211.68(b), three of them would modify the

wording. The comments suggested that the revised regulation does not accommodate the accepted use of validated computerized drug production and control systems.

FDA declines to amend the rule as suggested by the comments. The agency believes that the wording in the revised rule adequately encompasses the use of validated computerized drug production and control systems.

3. Two comments questioned the need for human verification of operations that are performed by validated computer systems. Both listed other regulations that were not the subject of the proposed rule that required more than one person to verify certain manufacturing operations, apparently in an effort to show that additional personnel would be needed to comply with proposed § 211.68.

FDA notes that the revisions to § 211.68 do not impose any specific personnel requirements. The agency, however, is aware that computers are subject to malfunctions; for example, the abrupt loss of data due to a computer "crash" can be a disruptive experience and possibly result in the loss of crucial information regarding the manufacturing process. Less dramatic events, such as faulty data entry or programming, can also trigger a chain of events that result in a serious production error and the possible distribution of an adulterated product. Thus, while increasingly sophisticated system safeguards and computerized monitoring of essential equipment and programs help protect data, no automated system exists that can completely substitute for human oversight and supervision.

The proposed rule stated (56 FR 5671 at 5673), and FDA reiterates here, that while the degree of verification is left to the manufacturer's discretion, the exercise of such discretion, under § 211.68, requires the use of routine accuracy checks to provide a high degree of assurance that input to and output from a computer or related system are reliable and accurate.

The agency intends that each manufacturer will exercise reasonable judgment based on a variety of factors, including, but not limited to, the complexity of the computer or related system, in developing a method to prevent inaccurate data input and output.

## C. Expiration Dating

Proposed § 211.137(g) would exempt investigational drug products from expiration dating requirements provided appropriate stability studies demonstrate that such products meet

appropriate standards or specifications during their use in clinical investigations.

4. All comments supported the proposed revision of §211.137. Two comments, however, recommended changes to clarify the labeling requirements for new drug products for investigational use that are to be reconstituted at the time of dispensing. One comment suggested language specifying the requirement's application to new drug products for investigational use to avoid confusion with § 211.137(c), which applies to all drug products that are to be reconstituted at the time of dispensing.

The agency agrees with these comments and has revised the rule

accordingly.

5. Proposed § 211.137(g) also deals with new drug products for investigational use that are to be reconstituted at the time of dispensing. The proposed regulation stated that labeling of such products would be required to bear expiration "dating" for the reconstituted drug product. One comment suggested changing the proposed requirement instead to require the labeling to bear expiration "information" for reconstituted drug products.

The requirement that expiration "information" be placed in the labeling of a drug product is found at § 211.137(c), and FDA agrees that this requirement should also apply to § 211.137(g). The final rule has been revised accordingly.

6. One comment recommended that the proposed exemption be extended to other clinical supplies not subject to IND requirements that are distributed for limited clinical testing, such as internal testing or evaluation in laboratories or for market research. Examples cited included drugs subject to over-the-counter drug monographs or **Drug Efficacy Study Implementation** 

requirements.

The agency does not agree that clinical supplies not subject to IND requirements should be exempt from expiration dating. The revision recognizes that for IND products it is often difficult or impossible to obtain the data upon which expiration dates are based. IND products are, therefore, exempt from expiration dating requirements provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations.

## D. Reserve Samples

As previously noted, proposed § 211.170(b) would clarify FDA's intent