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PART IV:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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HUMAN BLOOD AND BLOOD PRODUCTS

Collection, Processing and Storage

Title 21-Food and Drugs

CHAPTER I-FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

{Docket No. 75N-0240}

PART 606-CURRENT GOOD MANUFACTURING PRACTICES FOR BLOOD AND BLOOD COMPONENTS

PART 640-ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

Final Regulations for Collection, Processing and Storage

The Commissioner of Food and Drugs is issuing final regulations concerning good manufacturing practices for blood and blood components, effective December 18, 1975.

Proposed good manufacturing practices (GMP) regulations for the collection, processing, and storage of blood and blood components, intended to minimize the dangers of hepatitis in blood-based therapy and to assure the production of blood and blood components of uniform high quality throughout the nation, were published in the FEDERAL REGISTER of May 28, 1974 (39 FR 18614). The proposed regulations applied to all blood banks, transfusion facilities, plasmapheresis centers, compatibility testing establishments and all other facilities that process blood or blood components regardless of whether they were intended for interstate or intrastate commerce use. Interested persons were given until August 26, 1974 to file written comments with the Hearing Clerk, Food and Drug Administration, regarding the proposal.

Ninety-five letters, some containing a number of comments, were received. Many general comments were addressed to statements in the preamble. Most of the substantive comments concerned various specific provisions of the proposed regulations and contained recommended changes. Many comments encouraged greater specificity. Others indicated that the scope and intent of the proposed regulations were misinterpreted. To promote clarity and specificity, numerous nonsubstantive changes have been made. One of these nonsubstantive changes is a redesignation of the proposal to conform to an agency-aide format for good manufacturing practice regulations. The section numbers as originally proposed and their corresponding, redesignated numbers are as follows:

May 1974 Proposal:	Redesignated as
606.3	606.3
606.19	606.20
606.10	606.40
606.11	606.60
606.12	606.65
606.15	606.100
606.16	606.110
606.30	606.120
606.18	606.140
606.17	606.151
606.40	606.160
606.41	606.165
606.45	606.170

Throughout this preamble, the new section numbers have been used. The comments and recommendations re-

ceived and the Commissioner's conclusions concerning them are set forth of below.

GENERAL COMMENTS

1. Three comments strenuously objected to the phrase "good manufacturing practice" for the collection, processing, and storage of blood and blood components. It was argued that blood and blood components are not manufactured, and are not subject to sales taxes or implied warranties as are "manufactured" products. Rather, blood is produced by the donor and made available to the recipient. It was suggested that more appropriate terminology be used in place of the phrase "current good manufacturing practice."

The Commissioner advises that the term "manufacture" is applicable to blood and blood components. Blood is manufactured by the human body and requires further processing before it can be safely transfused into a recipient.

Blood intended for use in the diagnosis, cure, mitigation, treatment, and prevention of diseases in man is a drug as defined in section 201(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)). Section 501(a) (2) of the act (21 U.S.C. 3511 states, in part, that a drug shall be deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing and holding do not conform to, or are not operated or administered in conformity with, current good manufacturing practice to assure that such drug meets the requirements of the act.

In addition, blood is specifically identified as a biological product subject to regulation Pursuant to the Public Health Service Act (42 U.S.C. 262). Section 351 (a) (1) of this act uses the term "propagated or manufactured and prepared" for all biological products, including blood and blood components. The term "manufacture" is defined, in part, in § 600.3(u) (21 CFR 600.3(u) to mean all steps in the propagation of manufacture and preparation of products. The biologics regulations prescribe requirements concerning all aspects of the manufacture of blood even before it is removed from the donor: e.g., §§ 640.3 and 640.63 (21 CFR 640.3 and 640.63) concern criteria for donor suitability.

Accordingly, the Commissioner rejects the comments, and the term "good manufacturing practices" remains in the regulation, consistent with existing terminology in applicable laws and regulations.

2. One comment objected to the classification of blood transfusion as a human tissue transplant on the basis that the science and technology of tissue and organ transplants differ fundamentally from blood transfusion. Three comments objected to the classification of blood as a drug.

The Commissioner rejects these comments. Blood is considered a tissue by the scientific community and is classified as such by most histology textbooks. As has been set forth at length in the preamble to the proposal for these regulations and

in the final order concerning registration intrastate blood banks, published in the FEDERAL REGISTER of January 31, 1973 (38 FR 2965), blood is unquestionably a drug within the meaning of the Federal Food, Drug, and Cosmetic Act. The comments provide no information or data as a basis for the Commissioner to reconsider the classification of blood as both a tissue and a drug. Accordingly, no changes are made in the classification of blood as identified in the preamble of the Proposal.

3. Three comments implied that post-transfusion hepatitis cannot be controlled by promulgating the proposed regulation, but rather by developing consistently accurate methods to detect hepatitis B surface antigen (HB-Ag) in blood, which is the cause of osttransfusion hepatitis in blood recipients.

The Commissioner recognizes that the promulgation of good manufacturing practice regulations alone may not completely eliminate the incidence of post-transfusion hepatitis. The Commissioner has concluded that these regulations, together with the final order published in the FEDERAL REGISTER of July 15, 1975 (40 FR 29706) requiring hepatitis testing of a third generation sensitivity, will significantly reduce the incidence of post-transfusion hepatitis. Moreover, these regulations are also designed to assure the production of blood of uniform high quality, and it is well recognized that properly controlled processing procedures are a first and basic step to accomplishing this purpose.

4. Two comments suggested that Food and Drug Administration (FDA) inspections be waived whenever a blood establishment has been inspected by nongovernment organizations such as the American Association of Blood Banks (AABB), the College of American Pathologist% or the Joint Commission on Accreditation of Hospitals.

The Commissioner advises that section 510 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360) requires that the FDA inspect intrastate establishments that process drugs, including blood products. The biologics regulations require that interstate manufacturers of all biological products be inspected prior to the issuance of a license. Neither of these provisions authorizes delegation of inspection responsibilities to a nongovernment organization. Furthermore, the Commissioner concludes that independent inspection of establishments by both the FDA and nongovernment organizations will promote safety and will help to assure a high quality product. Accordingly, the Commissioner rejects these comments.

5. Two comments noted that the proposed regulations are more general in tone than the standards of the AABB. The comments suggested that the FDA accept the AABB standards in their entirety or that the FDA regulations and the AABB standards be combined, since the standards of the AABB already have achieved national, if not world wide, acceptance.

As indicated in the preamble of the proposal, the Commissioner intends that

the proposed regulations be applicable to blood banks, transfusion facilities, plasmapheresis centers, compatibility testing establishments and any facility that processes blood and blood components. To anticipate standards of operation for any facility that processes blood and blood components, the proposed GMP regulations must of necessity be broader in scope than the standards of the AABB, which are directed primarily to blood banks and transfusion services. Accordingly, the Commissioner rejects these comments. The Commissioner notes, however, that §606.100(d) Standard operating procedures provides that AABB manuals may be utilized consistent with the standards and guidelines established by these regulations.

6. One comment suggested that the proposed regulations be divided into two sections, the first to apply to blood banks and the second to blood depositories.

The Commissioner concludes that the proposed division of the regulations would not enhance clarity or promote the intent to assure the manufacture of products that are safe, pure, potent, and effective. Accordingly, the comment is rejected.

7. One comment stated that FDA should give priority to updating existing outdated regulations for products currently subject to its regulatory control before promulgating these new regulations.

The Commissioner concludes that priority must be given to amendments on the basis of their potential impact on the protection of the public health. These final regulations are of primary importance since they implement the provisions of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act for the first time for all blood establishments to assure that all blood and blood components on the market are safe, pure, potent, and effective. Moreover, the quality of currently marketed licensed products is sufficiently high under existing regulations to protect the public. And while the Commissioner recognizes that certain existing regulations need updating, an ongoing review of these regulations has resulted in recently published final orders and/or proposals regarding hepatitis testing of third generation sensitivity, platelet concentrate, normal serum albumin, plasma protein fraction and other blood products.

8. One comment noted that the preamble of the proposal requires that products meet all applicable standards prescribed in the biologics regulations. As a result, it was pointed out that the 28-day storage of blood approved by the State of Massachusetts conflicts with the 21-day dating period prescribed in 4610.53 (21 CFR 610.53) for Whole Blood (Human) collected in anticoagulant citrate phosphate dextrose solution (CPD). The comment suggested that the satisfactory experience obtained by the State of Massachusetts from its use of the 28-day storage period should be used as a basis for changing the 21-day dating period prescribed in § 610.53.

The Commissioner believes that a maximum dating period of 21 days for Whole Blood (Human) is practical and necessary to assure that only fresh whole blood is available for therapeutic use. Extension of the dating period would encourage storage of blood for an additional 7 days. Furthermore, the Commissioner has been advised that an amendment to the Massachusetts regulation is currently pending to reduce the storage period to 21 days. Accordingly, the comment is rejected.

DEFINITIONS

9. Two comments stated that a number of the requirements prescribed in proposed §§ 606.65, 606.100, 606.120 and 606.151 are not applicable to the manufacture of in vitro diagnostic products. For this reason, the comments suggested that the definition of "blood" in proposed § 606.3(a) be amended to exclude products intended as in vitro diagnostic reagents and that separate regulations be promulgated for them.

The regulations are generally applicable to all blood products, including in vitro diagnostic products. Significantly, proposed §§ 606.65, 606.100, 606.120, and 606.151 provide exemptions for requirements not applicable to in vitro diagnostic and other nontransfusion blood products. Accordingly, the Commissioner finds that separate regulations for in vitro diagnostic products are not necessary and no change is made in § 606.3(a) as proposed.

10. One comment concerning proposed § 606.3(b) stated that the definition of "unit" could be 5 to 10 milliliters. The comment gave no indication of an objection to the definition.

The Commissioner confirms that a unit would include volumes of 5 to 10 milliliters. Such small volumes are occasionally obtained from donors and infused into infants, often without antecedent testing for HBsAg or a serological test for syphilis. Additionally, small volumes of blood are used for the hyperimmunization of antiserum donors. The Commissioner concludes that infants and antiserum donors, should receive the high standard of protection offered by the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. Accordingly, the definition of a unit includes any volume of blood used for transfusion, and such blood is subject to the applicable requirements of the regulations.

11. Two comments requested that the regulations be amended to permit plateletpheresis and leukopheresis procedures. These comments are discussed in item 49 of this preamble. Concomitant with the Commissioner's response to these comments, § 606.3 of the final regulations has been amended to include definitions for plateletpheresis and leukopheresis in paragraphs (f) and (g), respectively; Proposed paragraphs (f), (g), and (h) are redesignated (h), (i), and (j) in the final order. Additionally, § 606.100(b) (17) has been added in the final regulation to require that the Standard Operations Procedure Manual describe the

plateletpheresis and leukopheresis Procedures used.

12. One comment stated that the definition of processing in proposed § 606.3(g) (redesignated § 606.3(i)) is not consistent with the customary use of the term in blood banking, i.e., the term does not ordinarily include procedures prior to the collection of blood, the collection of blood itself, or compatibility testing.

The Commissioner recognizes that the term has vernacular connotations in blood banking. Accordingly, the definition of processing has been modified in the final regulation to be consistent with the customary use of the term in blood banking.

13. One comment indicated that proposed § 606.3(h) (redesignated § 606.3(j)) inferred that compatibility tests are synonymous with cross-matching. The comment stated that compatibility tests include, but are not limited to, crossmatching.

The Commissioner does not intend to infer that compatibility tests are synonymous with crossmatching. The term "crossmatching" was added for clarity, since some blood banks use the term "crossmatching" while others use the term "compatibility test" when referring to the same serological test. However, since there appears to be confusion in the interpretation of the paragraph, the Commissioner has deleted reference to the term "crossmatching" in the final regulation.

PERSONNEL

14. Six comments concerning the introductory paragraph of proposed §606.20 suggested that the entire operation of a blood facility be under the direction of a qualified licensed physician and not a designated qualified person as prescribed in the proposed regulation. The comments stated that since blood banking is the practice of medicine, only a physician is qualified to direct a blood establishment.

The Commissioner intended that the qualified person be required to exercise control of the blood establishment consistent with the responsibility prescribed in § 600.10 (21 CFR 600.10) for a "responsible head". While the regulations do not exclude a physician from exercising these responsibilities, the Commissioner believes that nonphysicians with adequate training and experience are capable of performing such responsibilities. Past records of licensed establishments indicate that blood establishments having a nonphysician as the responsible head perform as well as those establishments having a physician as the responsible head. The Commissioner recognizes that certain responsibilities must be performed or supervised by a qualified licensed physician. Concomitantly, the regulations reflect such requirements in §§ 640.3, 640.61 and 640.62 (21 CFR 640.3, 640.61 and 640.62). Accordingly, the Commissioner rejects the comments. However, the Commissioner has revised the paragraph to clearly reflect the responsibilities of the person designated as director of the establishment. Additionally, the intro-

ductory paragraph has been designated paragraph (a). The proposed paragraphs (a) and (b) have been redesignated paragraphs (b) and (c) respectively.

15. Four comments concerning proposed § 606.20(a) (redesignated as § 606.20(b)) requested that the personnel qualification requirements be specified in the regulation.

The Commissioner intends to conduct a review of qualification requirements imposed by blood establishments for their medical and technical staff. Upon completion of the review, the commissioner will be in a position to make practical, specific recommendations concerning personnel qualifications requirements. In the interim, each blood establishment must continue to establish its own standards and training requirement consistent with the basic requirements of skills and knowledge of assignments set forth in these regulations. Accordingly, the comment is rejected.

16. Eight comments concerning proposed § 606.20(b) (redesignated § 606.20(c)) requested clarification concerning persons whose presence can adversely affect the safety and purity of the products. The comments especially indicated concern that the regulation might exclude hepatitis B surface antigen carriers from working in a blood establishment.

The Commissioner is not aware of any data that would implicate transmission of hepatitis B surface antigen to donors or blood products by personnel who are carriers of the antigen under the customary conditions of performance of their duties. Consequently, such personnel are not expected to adversely affect the safety and purity of the products, and it is not intended that they be excluded from areas of blood processing. Rather, the regulation is intended to exclude from the processing area, persons who may distract the attention of clinicians or technicians from the performance of their duties and persons who, by their very presence in the processing area, are capable of affecting the safety and purity of the product. Examples of the latter include personnel moving from the HBsAg testing area to the processing area without taking necessary precautions and persons known to have contagious respiratory ailments. The Commissioner believes that the regulation is clear and precise. Accordingly, the comments are rejected and no change is made in the final order.

FACILITIES

17. One comment concerning proposed § 606.40(a) (2) requested further clarification of the phrases "adequate space", "minimal exposure" and "unrelated activities."

The Commissioner utilized these phrases to indicate that the facility's space must be conducive to the safety of the donor and the manufacture of a product that is safe, pure, potent and effective. More specific phrases were not used because the regulations are applicable to any facility that processes blood and blood components, and it is impossible to specify the exact size, location,

arrangement, lighting and equipment requirements without information concerning the specific process, number of donors, etc. For clarity, however, the Commissioner has changed the phrase "unrelated activities and equipment" to "activities and equipment unrelated to blood collection."

18. Two comments requested that proposed § 606.40(a) (3) be amended to require space for quarantine storage only for blood or blood components that give questionable serological test results. The comments suggested that there is no need to hold products in quarantine storage pending completion of all tests, as proposed.

The intent of quarantine storage is to isolate those units of blood and blood components that have been identified as potentially hazardous. Isolation assures that such products will not be used accidentally. The Commissioner agrees that untested blood should not be categorized as having the same safety risks as tested blood yielding questionable test results. The Commissioner concludes that untested blood and blood components need not be held in quarantine storage. Accordingly, § 606.40(a) (3) has been revised and a new paragraph (a) (4) has been added in the final regulation to differentiate storage space requirements for tested and untested blood. The proposed paragraphs (a) (4) through (a) (8) have been redesignated (a) (5) through (a) (9), respectively.

19. The Commissioner has also amended proposed § 606.40 by adding the word "quarantine" to the beginning of proposed paragraph (a) (5) (redesignated as paragraph (a) (6)) to be consistent with the discussion of the comment in item 18 of this preamble concerning the storage of products that may be potentially hazardous. Similarly, proposed paragraph (a) (6) (redesignated paragraph (a) (7)) has been amended consistent with the discussion in item 12 of this preamble concerning the definition of processing.

20. One comment suggested that proposed § 606.40(b) be clarified to indicate whether the word "screening" in the phrase "screening of open windows and doors" is intended to mean visual screening.

The Commissioner has used the word in its common or usual sense in association with doors or windows: namely, a partition, usually of wire or plastic mesh, to protect the facility from insect or rodent infestations. The Commissioner concludes that paragraph (b) adequately conveys this meaning. Accordingly, the comment is rejected and no changes are made in the final regulation.

21. Two comments concerning proposed § 606.40(c) suggested that the requirement to provide handwashing facilities in work areas could be interpreted to require that each work area, whether large or small, must have its own handwashing facility.

The Commissioner intends that handwashing facilities be convenient for personnel. However, the Commissioner recognizes that the paragraph may be mis-

interpreted as suggested in the comment. Accordingly, § 606.40(c) of the final regulation more clearly conveys the Commissioner's intent.

22. One comment interpreted proposed § 606.40(d), concerning the safe and sanitary disposal of trash and items used during Processing of blood and blood components, as not contemplating anything more than Proper disposal through the local refuse disposal system. The comment suggested that if anything further is required, the Proposed rule should be republished in specific terms for further opportunity for comment.

The Commissioner advises that trash and other items used during the collection, processing, and compatibility testing of blood and blood components must be disposed of in a safe and sanitary manner. To ensure safe and sanitary disposal, all potentially infectious material must be autoclaved, incinerated, or otherwise sterilized to preclude contamination of the environment. These procedures do not require special or extraordinary disposal systems and no further publication with an opportunity for comment is warranted. Additionally, the Commissioner notes that the proposal did not specifically require the safe and sanitary disposal of blood and blood components found to be unsuitable for use. However, it is consistent with the obvious intent of the regulation, that such blood and blood components, likewise, should be discarded in a safe and sanitary manner to protect the public from the potential hazard that could be caused by introducing infectious material into the public waste disposal systems. Accordingly, § 606.40(d) of the final regulation more specifically identifies those items requiring safe and sanitary disposal.

EQUIPMENT

23. Five comments concerned the requirement in proposed § 606.60 that equipment be calibrated or tested on a regularly scheduled basis. Three comments requested, for clarity, examples of equipment requiring calibration or testing and the frequency at which they must be calibrated or tested. Two comments objected to the requirement on the basis that certain equipment cannot be calibrated because the design characteristics are not made available by the manufacturer of the equipment.

The Commissioner accepts the comments requesting clarification of the requirement. Accordingly, § 606.60 in the final regulation provides a list of examples of equipment to be calibrated, including the characteristics of the equipment to be calibrated, such as weight, temperature speed, etc., and the frequency of calibration. The objection that certain equipment cannot be calibrated or tested on a regularly-scheduled basis because the design characteristics are not made available by the manufacturer is rejected by the Commissioner. The use of accurate and reliable equipment is essential to ensure compliance with the requirements for the manufacture of products that are safe, pure, potent and

effective. For this reason: the Commissioner concludes that all equipment used in a blood establishment must meet the specifications for producing the intended effect in the manufacture of blood and blood components. To assure that any piece of equipment is operating properly, it must be tested on a regular basis and adjusted when necessary. If the equipment is faulty and cannot be repaired by the blood establishment, it must not be used by the blood establishment until repaired by other sources, or the piece of equipment may be replaced with one found to operate as required.

24. One comment suggested that Proposed § 606.60 be amended to delete the phrase "official requirements" because official requirements for equipment have not been established.

The Commissioner intended that the phrase "official requirements" relate not to equipment, but rather to requirements such as weight, temperature, etc., prescribed for products in the regulations for blood and blood products. Accordingly, § 606.60 in the final regulation clarifies the intent of the phrase "official requirements."

25. Three comments concerning Proposed § 606.60 suggested exempting from the sterilization requirement, disposable material that is already sterile when purchased by the blood establishment.

The Commissioner agrees that there is no need to resterilize disposable material that is sterile when purchased, and the regulations do not require that such material be resterilized. Furthermore, the subject regulation concerns equipment rather than material. Accordingly, no change is made in the regulation.

SUPPLIES AND REAGENTS

26. The title of proposed § 606.65 has been changed in the final regulation from "Materials" to "Supplies and reagents" for clarity and specificity.

One comment concerning § 606.65 (a) suggested that an appropriate method be recommended for confirming pyrogenicity of supplies, such as blood container and donor sets, which the manufacturer claims are pyrogen free.

The Commissioner believes that ultimate responsibility for the claim that supplies are pyrogen-free should rest with the manufacturer of the supplies and not with the blood establishment. Accordingly, the comment is rejected and no special reference is made in § 606.65 (a) to a method for determining pyrogenicity.

27. One comment concerning proposed § 606.65 expressed concern regarding the requirement that all final containers for blood and blood components not intended for transfusion be made of material that will not interact with their contents to affect adversely the safety, purity, potency and effectiveness of the product. It was suggested that FDA inspectors might demand proof that the final container does not interact with its contents.

The Commissioner advises that with respect to containers for blood and blood products intended for transfusion or for further manufacture into injectable

products, substantial evidence establishing the safety and effectiveness must be submitted to the FDA by the manufacturer of the container for premarketing clearance. However, final containers for blood and blood components not intended for transfusion or for further manufacture of injectable products only need to be clean and free of surface solids and other contaminants and are not subject to premarketing clearance and approval by FDA. These exemptions do not apply when there is any possibility of the collected blood, or any part thereof, being returned to the donor.

28. One comment concerning proposed § 606.65(b) suggested that, in addition to the required inspection of containers prior to use, the container also be visually inspected for damage or evidence of contamination immediately after filling.

The Commissioner recognizes that a small puncture and certain types of contamination will be more evident after the container is filled. Accordingly, he accepts the suggestion and has added a provision to § 606.65(b) concerning visual inspection of containers immediately after filling.

29. Three comments concerning proposed § 606.65(b) noted that discoloration of certain collection and satellite containers is normal after sterilization. The comments suggested that the requirement concerning discoloration of the container either be deleted or revised to reference abnormal discoloration.

The Commissioner agrees that a certain amount of discoloration in plastic containers is normal and does not indicate a substandard container. Accordingly, the Commissioner accepts the suggestion and has amended § 606.65(b) by qualifying the word "discoloration" with the word "abnormal."

30. Ten comments concerning proposed § 606.65(c) objected to the requirement that representative samples of solutions or reagents susceptible to contamination be tested on a regularly scheduled basis to determine freedom from bacteria. It was argued that, generally, sterility of such unopened products is guaranteed by the manufacturer and therefore should not require further testing by the blood establishment. Additionally, it was noted that a vial of solution or reagent is normally used more than once. Consequently, some contamination of an opened vial is inevitable.

The Commissioner agrees that the manufacture of the solution or reagent should be responsible for the sterility of an unopened product. Furthermore, the Commissioner recognizes that the usual contamination of an opened vial of solution or reagent will not seriously affect its potency or effectiveness. The purpose of the regulation is to ensure potency and effectiveness of solutions and reagents. Such assurance is obtained by the additional requirement in the same paragraph that samples of solutions or reagents liable to changes in concentration be tested on a regularly scheduled basis to determine their strength. In view of the testing for reagent reactive qualities provided by the regulations, the Commis-

sioner has concluded, on balance, that the requirement concerning sterility testing may be deleted from § 606.65 (c).

31. Two comments concerning Proposed § 606.65(c) expressed dissatisfaction with the need to assay solutions or reagents periodically for changes in concentration. One comment suggested that examples be given of solutions and reagents to be tested.

The Commissioner concludes that regularly scheduled testing of solutions and reagents for concentration is necessary to ensure adequate effectiveness of these products. Such testing is particularly important after storage or intermittent periods of use when the Product can be expected to lose some of its reactive qualities. Quantitative tests need not be employed to demonstrate the capacity of the reagent to Perform as required. Rather, suitably chosen control procedures may be used, provided such procedures are adequately described in the blood establishment's Standard Operating Procedures Manual. Accordingly, the final regulation retains the requirement to test regularly solutions and reagents to determine their concentration. However, to promote clarity and specificity, § 606.65(c) has been amended to provide a list containing reagents and solutions that shall be tested on a regularly scheduled basis and the required frequency of testing.

22. One comment interpreted proposed § 606.65(d) (now incorporated into § 606.160) to include the requirement that results of visual inspection of blood containers be recorded. The comment stated that it is unnecessarily burdensome to maintain such records and that only defects of containers need be recorded.

The Commissioner finds that the interpretation of the paragraph is incorrect. The intent of the proposed regulation is not to record the condition of each blood container, but rather to record the identity and disposition of containers that are not suitable for use. To clarify the requirements concerning records, the Commissioner has provided in § 606.160 a comprehensive list of records that must be maintained by the blood establishment.

33. Four comments concerning Proposed § 606.65(d) (1) (redesignated § 606.160(b) (7) (v)) objected to the requirement for maintaining records of the lot number, expiration date, and date of receipt of each type of supply or reagent received from each manufacturer.

The Commissioner concludes that such records are necessary, together with processing records and compatibility records, to investigate and resolve problems that may arise from the use of faulty reagents or supplies employed in the manufacture of blood and blood components. Accordingly, the Commissioner rejects the comments and no change is made in § 606.160(b) (7) (v).

34. Four comments concerning Proposed § 606.65(d) (2) (redesignated § 606.160(a) (2)) indicated that the requirement to keep specific records relating the lot numbers of reagents and up-

plies to the final product requires an unnecessary amount of documentation.

The Commissioner advises that records must be kept to identify the reagent and other material employed in the Production of each lot or unit of final blood product. However, the commentor apparently interpreted § 606.65(d) (2) as requiring that the lot numbers of reagents and supplies employed in the production of a final product be recorded in a specific manner such as a log book. No one format for these records is specified. Rather, as prescribed in § 606.160(a) (2), appropriate records must be available from which to determine the lot number of reagents and supplies used for specific lots or units of final blood product.

35. One comment concerning proposed § 606.65(d) (3) (now incorporated into § 606.160(b) (5) (ii) and (b) (7) (vi)) interpreted the proposed paragraph as requiring that blood establishments repeat the tests performed by the manufacturer of the material. The comment indicated that most blood establishments do not have the equipment or expertise to retest purchased materials.

The Commissioner advises that the comment incorrectly interpreted the requirement. The regulation does not require that the blood establishment repeat the test performed by the manufacturer of the material. Rather, the intent of the regulation is to require a record of performance checks of equipment and reagents as prescribed in § 606.160(b) (5) (ii) of the final regulations.

36. The requirements in proposed § 606.65(e) concerning testing of reagents for potency and the maintenance of records have been transferred to §§ 606.65(c) and 606.160(b) (7) (i), respectively. The paragraphs in § 606.65 have been renumbered accordingly.

37. Eight comments concerning proposed § 606.65(f) (redesignated § 606.65 (d)) generally agreed with the principle of storing the material in such a manner that the oldest is used first. However, four comments suggested that the requirement should not apply to reagents or supplies bearing an expiration date, as long as these materials are used within the dating period. Additionally, four comments questioned the need to promulgate such a requirement.

The Commissioner agrees that there is no need to require that products bearing a dating period be used on an "oldest-first" basis, in that these products have been tested and shown to maintain adequate potency and effectiveness during the entire length of the dating period. Consequently, there is no objection to using such products any time within the dating period. However, labels do not generally indicate the rate of loss of potency and effectiveness of products not bearing a dating period. To assure no loss of potency or effectiveness, these materials should be used on a first-in-first-out basis. Accordingly, § 606.65(d) has been amended to apply to products that do not bear an expiration date.

36. One comment concerning proposed § 606.65 (h) (redesignated § 606.65 (f)) re-

quested that the word "possible" be changed to "practical."

The Commissioner believes that disposability is an effective means of reducing the spread of infectious disease, especially the spread of hepatitis B virus. The accrued benefits of using disposables override all other considerations of practicality. Accordingly, the comment is rejected and no change is made in the regs.

STANDARD OPERATING PROCEDURES

39. It has come to the attention of the Commissioner that § 606.100(a), as proposed, could be misinterpreted as requiring that establishments not subject to licensure must comply with those specific provisions in Part 640 (21 CFR Part 640) which, by their terms, apply only to licensed establishments. Accordingly, Proposed § 606.100(a) is amended in the final regulation to provide that the references in Part 640 relating to licenses, licensed establishments and submission to and approval by the Director, Bureau of Biologics, are not applicable to non-licensed establishments.

Of course, the standard operating procedures that unlicensed establishments are required by these regulations to follow must comply with the substantive procedures for specific blood products set forth in Part 640.

40. One comment concerning proposed § 606.100(b) objected to the requirement that blood establishments maintain written standard operating procedures. The comment suggested that the art of blood banking may be downgraded if all steps were required to be written.

The Commissioner disagrees with this comment. The manual is intended to describe the best techniques, procedures and policies developed by blood banking practitioners. The Commissioner believes that the guidance provided to personnel from use of the manual, together with personnel development concerning attentiveness to detail, experience, training, common sense, etc., can only upgrade the art of blood banking.

41. Another comment concerning proposed § 606.100(b) requested guidance for the collection of blood intended for autologous transfusion, a transfusion in which the patient is infused with his own blood that was withdrawn on a previous occasion.

The Commissioner will issue at another time proposed additional standards governing products intended for autologous transfusion. In the meantime, any facility that collects blood for autologous transfusion must describe in the Standard Operating Procedures Manual, the steps followed from collection to distribution of such units. The manual of each licensed blood establishment is reviewed by the Bureau of Biologics at the time of licensure to assure that all procedures described therein are safe and result in a product that is safe, pure, potent and effective. Manuals of unlicensed establishments are subject to review during inspection by the FDA, but need not be submitted to the Bureau of Biologics for approval. To promote specificity and

clarity of the regulation, the Commissioner has amended § 606.100(b) by identifying homologous transfusion, autologous transfusion, and further manufacture of blood and blood components as procedures that must be described in the written Standard Operating Procedures Manual.

42. Three comments concerned proposed § 606.100(b) (5). Two of these comments objected to weighing each unit of blood on the basis that it is costly and unnecessary. The comments suggested that quality control of equipment will assure collection of blood within an acceptable range. The third comment suggested that the regulation be amended to provide a recommendation concerning the equipment to be used for weighing;

The Commissioner believes that the comments misinterpreted the regulation. The intent of the regulation is to ensure that the quantity of blood taken from the donor does not exceed the volume permitted by regulation. This is normally accomplished by the use of an in-process device which, based upon weight, mass or volume; signals the completion of the donation. Indeed, the regulation does not anticipate the weighing of each unit of blood when the in-process device has been demonstrated to be accurate and reliable. Rather, the regulation anticipates written procedures concerning use and maintenance of the device to assure its accuracy and reliability. Finally the Commissioner concludes that there is no need to recommend specific equipment to be used for measuring the quantity of blood removed from the donor. The specific equipment used by the blood establishments should be described in the written Standard Operating Procedures Manual and will be reviewed during inspection by the FDA. Accordingly, no change is made in § 606.100(b) (5).

43. Two comments concerning proposed § 606.100(b) (7) noted that after publication of this proposal, a notice was published in the FEDERAL REGISTER of July 9, 1974 (39 FR 25233) proposing to amend § 610.40 **Tests for hepatitis B surface antigen** (21 CFR 610.40) to require testing of blood for hepatitis B surface antigen by a method of third generation sensitivity. The comments recommended that the requirement to use a method of third generation sensitivity be reflected in § 606.100(b) (7).

The Commissioner accepts the comments and § 606.100(b) (7) has been amended accordingly.

44. The Commissioner has added a new paragraph (b) (9) to proposed § 606.100 concerning procedures for investigating adverse reactions. The proposed paragraph, (b) (9) and those following are renumbered accordingly. The reason for adding the new paragraph is that Proposed § 606.170 **Adverse reaction file** requires that a thorough investigation be made for each reported adverse reaction. The Commissioner concludes that the procedures for carrying out the investigation should be described in the Standard Operating Procedures Manual to Provide guidance to personnel involved in the investigation.

45. Two comments concerning proposed § 606.100(b) (10) (redesignated § 606.100(b) (11)) indicated that the requirement to identify the length of expiration dates assigned for all final products may cause confusion since some products such as Source Plasma (Human) and Recovered Plasma (Human), do not have expiration dates.

The Commissioner accepts the comments. Accordingly, to clarify the regulation, the phrase "if any" is added after the phrase "Length of expiration date" in § 606.100(b) (11).

46. The Commissioner has added a new paragraph (b) (18) to proposed § 606.100 concerning procedures for preparing recovered (salvaged) plasma. The paragraph is added in response to a number of general comments requesting greater specificity in the regulations.

47. Comments objected to proposed § 606.100(c), which they interpreted as requiring a single comprehensive review of all applicable records at the time of distribution of blood or blood components. Another comment indicated that the paragraph seemed to be directed toward blood products rather than fresh blood or fresh blood components.

The Commissioner concludes that the comments have misinterpreted the intent of the regulation. The regulation requires that the records pertaining to a product be reviewed prior to distributing the product, not necessarily immediately prior to distribution. The review, or portions of the review, may be conducted at appropriate periods during or after blood collecting, processing, compatibility testing and storing. Additionally, the regulation is intended to apply to establishments preparing any blood product, including fresh blood and fresh blood components. Accordingly, the Commissioner has amended § 606.100(c) to clarify the intent.

PLATELETPHERESIS, LEUKAPHERESIS AND PLASMAPHERESIS

48. Twenty-five comments concerned Proposed § 606.110 *Plasmapheresis*. Most of the comments were substantively the same as, or similar to, comments received in response to a notice published in the FEDERAL REGISTER of July 17, 1974 (39 FR 26161) proposing to expand the definition of Source Plasma (Human) in Part 640 to include all products collected by plasmapheresis, except Single Donor Plasma (Human) intended for intravenous use. The final regulations responsive to the July 17, 1974 proposal will prescribe requirements for Source Plasma (Human) intended for preparation of components for injection or for further manufacture into noninjectable products.

The Commissioner has determined that these good manufacturing practice regulations no longer need to prescribe specific requirements for plasmapheresis since proposed § 606.100 requires that the standard operating procedures must comply with the regulations for Source Plasma (Human) as presently drafted and as they may be amended. For continuity in the discussion relating to

plasmapheresis, the Commissioner will respond to the comments concerning plasmapheresis and proposed § 606.110 in the preamble to the final regulations concerning Source Plasma (Human) which will be published in the near future.

The Commissioner recognizes that in the meantime, provision should be made to permit the plasmapheresis of a donor who does not meet the requirements of §§ 640.63, 640.64 and 640.65 for the collection of plasma containing rare antibodies. Accordingly, the Commissioner has added a new paragraph (b) to § 606.110 to permit such plasmapheresis of a donor only with approval of the Director, Bureau of Biologics.

49. Two comments concerning proposed § 606.110 noted that neither the proposed regulation nor any of the existing biologic regulations prescribe the use of leukapheresis and plateletpheresis procedures for obtaining leukocytes or platelets, respectively, from a donor. The comments expressed concern that these procedures would no longer be permitted when needed for specific patients requiring repeated leukocyte or platelet transfusions.

The Commissioner advises that use of plateletpheresis as a source of Platelet Concentrate (Human) was provided for in the Additional Standards for Platelet Concentrate (Human), §§ 640.20 through 640.26 published in the FEDERAL REGISTER of January 29, 1975 (40 FR 4300). The use of the leukapheresis procedure, as indicated by the comment, is not presently prescribed by the existing biologic regulations.

The provisions prescribed in §§ 640.21 (c) and 640.22(c) (21 CFR 640.21(c) and 640.22(c)) of the Additional Standards for Platelet Concentrate (Human) require that when plateletpheresis is used, the criteria of donor suitability and collection procedure must have written approval of the Director, Bureau of Biologics. Such approval is granted only after the blood establishment has demonstrated that the criteria and procedures will assure safety of the donors. These provisions, however, may preclude the use of plateletpheresis by a hospital in emergency situations when a physician has determined that the recipient must be transfused with the platelets from a specific donor, but the donor does not meet the criteria of weight, blood pressure, etc., approved by the Bureau of Biologics in accordance with § 640.21(c).

The Commissioner recognizes that leukapheresis and plateletpheresis are important to a hospital for collecting large volumes of leukocytes and platelets, especially from a small number of donors who are selected because of the compatibility of their blood with that of the recipient. Indeed, the most medically desirable donors are often relatives of the recipient.

Leukapheresis and plateletpheresis involve the return of nearly all the plasma, plus the formed elements, minus the leukocytes or platelets, respectively. These procedures do not significantly reduce the oxygen-carrying, oncotic or volu-

metric capacities of the donor's circulating system. Therefore, use of these procedures presents no long-term risks that could not be assessed by a physician at the time of donation. The Commissioner believes that provision must be made in the regulations to permit use of these life-saving procedures.

Accordingly, proposed § 606.110 has been amended to permit the use of the leukapheresis and plateletpheresis procedure when (a) the physician has determined that the recipient must be transfused with the leukocytes or platelets from a specific donor (b) the procedure is performed under the supervision of a physician who is aware of the health status of the donor; and (c) the physician has certified in writing that the donor's health permits leukapheresis or plateletpheresis. Under such circumstances, the requirements prescribed in §§ 640.21(c) and 640.22(c) concerning prior approval of the criteria of donor suitability and the collection procedure of plateletpheresis by the Director, Bureau of Biologics, are waived. The Commissioner believes that such emergency provisions for plateletpheresis also should be reflected in the regulations governing the manufacture of Platelet Concentrate (Human). Accordingly, a new § 640.27 *Emergency provisions* is added to Platelet Concentrate (Human) regulations.

LABELING

50. One comment concerning proposed § 606.120(a) (1) suggested that the regulation be amended to permit a multilocation establishment to proof all labeling at one location. The comment interpreted the regulation as requiring that each location must proof the label against an approved final copy.

The Commissioner advises that the regulation was misinterpreted. The regulation does not prohibit a multilocation establishment from reviewing and proofing all labels at one location. Accordingly, no change is made in the regulation.

51. Two comments concerned proposed § 606.120(b). One comment recommended that the regulation be revised to require that labels applied by one blood service not be altered in any way by another blood service. The other comment recommended that the regulation be revised to permit a hospital to replace the original label, since the original label may be confusing to a physician who administers the product.

The Commissioner advises that the label information provided by the collection facility and the initial processing facility are necessary to identify and confirm that the product is safe, pure, potent and effective, and to facilitate the tracing of a product back to its original source. Indeed, the Commissioner did not anticipate that the regulation might be interpreted to imply that the original label may be removed, altered or obscured. Accordingly, to prevent any misinterpretation of the regulation, a sentence has been added to § 606.120(b) to prohibit any alteration of the original label. However, this does not preclude a hospital from adding further informa-

tion to a product container, provided the original label is not removed, altered or obscured. Accordingly, the Commissioner rejects the comment concerning replacement of the original label.

The Commissioner recognizes that under certain circumstances in the manufacture of blood components the original label of the source material must be altered to provide accurate identification of the proper name of the product. For example, after plasma is removed from Whole Blood (Human), the remaining product is Red Blood Cells (Human). Accordingly, § 606.120(b) is amended in the final regulation to permit altering of labels, as necessary, to reflect the proper name of the product and other required labeling information for the contents remaining in a container after blood components have been removed.

52. One comment concerning proposed § 606.120(b) (5) suggested that the necessary instructions and precautions for use be required for the directions circular only and not on the product label.

The Commissioner concludes that the requirement as proposed is consistent with §§ 610.60 and 610.61 (21 CFR 610.60 and 610.61) prescribing the information that must appear on the container and package labels of all biological products. Accordingly, the comment is rejected. However, the Commissioner recognizes that certain information, such as the formula of the anticoagulant solution in the container, need be contained only in an instruction circular. For this reason, the Commissioner is reviewing the present labeling requirement for all blood products with the intent of publishing a proposal in the near future concerning a revised uniform labeling requirement.

53. Two comments concerning proposed § 606.120(b) (7) recommended that distribution of instruction circulars for whole blood and blood components not be required. Another comment suggested that the instruction circular not necessarily accompany each unit of blood.

The Commissioner recognizes that those experienced in performing transfusions may not need to refer to the instruction circular each time a transfusion is given. However, the circular provides a valuable synopsis of the best available information on the uses, precautions and contraindications associated with the use of blood and blood components. This information may be utilized by interns and residents, as well as recently transfused patients. Moreover, labeling for these drug products must, pursuant to section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(f) (1)) bear adequate directions for lay use. Accordingly, the Commissioner rejects the comments recommending that distribution of the instruction circular not be required. The Commissioner did not intend, nor does the regulation imply, that the circular accompany each unit of whole blood. Rather, the regulation requires that circulars must be available in the collecting and transfusing facilities for reference, as needed, by transfusionists, interns, residents and patients.

54. Two comments concerning proposed § 606.120(b) (8) requested that a provision be added to permit the volume of a product in a container to vary by ± 10 percent from the volume stated on the label. Another comment noted that the quantity of product is normally not specified for certain products, e.g., Cryoprecipitated Antihemophilic Factor

The Commissioner acknowledges that certain measurement devices presently used by blood banks are accurate only within a 10 percent range. Consequently a unit of whole blood is recognized as being within ± 10 percent of the volume stated on the label. Since a discrepancy of ± 10 percent of the volume stated on the label does not affect the safety, purity, potency and effectiveness of the product, the Commissioner has amended the regulation to permit the quantity of product stated on the label to be accurate to within ± 10 percent. However, it should be emphasized that the amendment does not affect, in any manner, the maximum amount of whole blood, which by regulation is permitted to be removed from a donor, i.e., § 640.65(b) (4), (5) and (6) (21 CFR 640.65(b) (4), (5) and (6)). The Commissioner recognizes that it is impractical to determine the volume of Cryoprecipitated Antihemophilic Factor (Human) in a container, and proposed § 606.120(b) (8) is not intended to apply to this product. Rather, proposed paragraph (b) (9) is applicable and consistent with § 640.51(c) (6) (21 CFR 640.51(c) (6)) concerning Cryoprecipitated Antihemophilic Factor (Human), requiring that the quantity of source plasma, and kind and quantity of anticoagulant appear on the labeling. Accordingly, to ensure that there is no misinterpretation concerning the intent of proposed paragraph (b) (8), the Commissioner has added a phrase exempting this product from the requirement that the labeling indicate the quantity of product in the container and further providing that the ± 10 percent variance does not apply to Source Plasma (Human) for which precise weight measurement is regularly attained.

LABORATORY CONTROLS

55. Two comments concerning proposed § 606.140 requested that the regulation be revised to specifically define requirements such as "adequate" monitoring, "appropriate" specifications, and the like.

The Commissioner believes that each blood establishment should select its own specific laboratory control procedures applicable to the processes it performs, its equipment, personnel and other variable factors. The regulations are intended as a general guideline for use by a blood establishment in developing specific laboratory control procedures. There are available recognized laboratory control guides, such as Quality Control in Blood Banking, American Association of Blood Banks, 1973, or Myhre, B.A. and Quality Control in Blood Banking, Wiley and Sons Inc., NY 1974, which provide pro-

cedures for implementing the Standards set forth in these regulations. Accordingly, the comments are rejected.

COMPATIBILITY TESTING

56. Two comments concerning proposed § 606.151 argued that crossmatching is not, and should not, be within the province of the FDA, inasmuch as it is a procedure performed entirely within the hospital laboratory.

The Commissioner advises that in some instances community blood banks perform crossmatching procedures in place of the hospital laboratory. In addition, the Commissioner believes that his authority under the Federal Food Drug, and Cosmetic Act and the Public Health Service Act to regulate all aspects of blood and blood components processing and testing has been adequately documented in the preamble of the proposal. The Commissioner considers the crossmatching, as well as other 'compatibility tests to be as significant to blood as the general safety test described in § 610.11 (21 CFR 610.11) is to other biological products. Indeed, it is impossible for the Commissioner to assure the safety, purity and effectiveness of blood and blood products without the authority to assure that all compatibility tests are accurate and reliable.

57. Two comments concerning the introductory paragraph of proposed § 606.151 requested that the first sentence be deleted. The comments indicated that it is unreasonable for a small institution to require an entirely separate area for compatibility testing.

The Commissioner accepts the comments. It is not essential that an area be set aside for compatibility tests only. Rather, it is essential that compatibility testing be conducted in a work area that is arranged in an orderly manner so as to avoid mixups or contamination of the product. This requirement is already addressed in proposed § 606.40(a) (7). Accordingly, the Commissioner has deleted the first sentence from the introductory paragraph of § 606.151.

58. Three comments concerning proposed § 606.151(b) objected to the requirement that serum be less than 48 hours old for all compatibility testing. The comments suggested that there is adequate data in the literature to support use of serum older than 48 hours for such testing. Also, one comment suggested that the serum for compatibility testing should be less than 6 hours old.

The Commissioner prescribed the 48-hour limit on the basis of data demonstrating that antibodies in a blood recipient's serum 46 hours old can adequately be detected by compatibility testing. Accordingly, the commissioner rejects the comment suggesting that serum be less than 6 hours old. Serum samples stored at refrigerator temperatures beyond 48 hours may become contaminated with airborne microorganisms. Some microorganisms produce substances capable of agglutinating red cells and may, therefore, predispose serum to false positive agglutination reactions. Accordingly,

the Commissioner rejects the comment and no change is made in the regulations. However, the FDA is conducting a review of available data concerning compatibility testing with serum that is 72 hours old. Interested persons are encouraged to send such data, or references to such data, to the Director, Bureau of Biologics, 8800 Rockville Pike, Bethesda, MD 20014. The Commissioner will propose to extend the 48-hour limit to 72 hours or longer if available data support such extension.

59. Five comments concerning paragraph (c) and (d) of proposed § 606.151 suggested that the major crossmatch test include testing for hemolytic antibodies, as well as the already required agglutinating and coating antibodies.

The Commissioner intends that the major crossmatch test include testing for all antibodies of major concern. Hemolytic antibodies are of major concern but were inadvertently omitted in the Proposed regulation. Accordingly, the Commissioner accepts the comments and paragraphs (c) and (d) have been amended as suggested by the comments.

60. One comment concerning proposed § 606.151(d) requested that provision be made to permit screening of the donor's blood by any method that has been demonstrated to be at least equivalent to the antiglobulin method for determining the presence of agglutinating, coating and hemolytic antibodies. Included with the comment was data supporting use of an enzyme method proposed for use in place of the antiglobulin method.

The Commissioner believes that the regulation should anticipate the use of other methods that are equivalent to, or better than the antiglobulin method for demonstrating antibodies in the donor's blood. Additionally, the Commissioner concludes that the data submitted with the comment demonstrate that the enzyme method is at least equivalent to the antiglobulin method. Accordingly, § 606.151 (d) has been revised. In the final regulation to permit screening of a donor's blood by any method that will demonstrate agglutinating, coating and hemolytic antibodies.

61. Two comments concerning proposed § 606.151(d) suggested that the minor crossmatch test be required whether or not donor screening is performed. The comments indicated that the test is important as an additional check to assure that the Patient is given the proper blood. Another comment suggested that reference to the minor crossmatch be deleted and replaced with a requirement that all donor sera be tested by methods adequate to detect clinically significant antibodies. The comment stated that there are good reasons for the undesirability of performing the minor crossmatch and also inter se crossmatches. However, the specific reasons were not given.

As evidenced by the comments, there is disagreement within the scientific community concerning the advantages of the screening test versus the minor crossmatch test and the practical need to perform one of these tests if the other al-

ready has been performed. In light of this disagreement, and since the available data equally support advantages of either test procedure, the Commissioner, in the proposed regulation, has permitted use of the screening test or the minor crossmatch test as alternative testing procedures. No new data demonstrating that one testing procedure is superior to the other has been made available to the Commissioner. For these reasons, the Commissioner rejects the comment requesting that reference to the minor crossmatch test be deleted. The Commissioner believes that the major crossmatch test required by paragraph (c), together with a test designed either to screen the donor's serum or to reflect compatibility of the donor's serum with the recipient's red blood cells (minor crossmatch), are practical, necessary and adequate to protect the recipient from a transfusion with incompatible blood. Accordingly, the Commissioner also rejects the comment requesting that both screening and minor crossmatch tests be required prior to transfusion, and no change is made in the regulation.

62. Seven comments concerning proposed § 606.151(e) objected to the words "modified" and "safe" to describe the procedures for expedited transfusions in emergencies. The comments noted that in an emergency situation there is normally not enough time to conduct all required testing of the blood. Consequently, the blood cannot be determined to be as safe as blood processed under normal conditions.

The Commissioner recognizes the limited assurances provided by any emergency procedure and therefore accepts the comments, and the words "modified" and "safe" have been deleted from § 606.151(e) of the final regulation. The Commissioner notes that the comments interpreted the word "procedures" as strictly applying to the method of performing the crossmatch. However, it should be emphasized that the term "procedure" includes administrative procedures relating to emergency transfusions as well as the technical procedures.

RECORDS

63. Three comments concerning proposed § 606.160(a) (redesignated as § 606.160(a) (1)) requested clarification of the significant steps for which records must be maintained and questioned the need for maintaining certain records, especially those that identify the person performing the work.

The Commissioner has used the term "significant step" to mean any step that may affect the safety of the donor and recipient, or the safety, purity, potency and effectiveness of the product. For example, with respect to blood collection, the amenities provided the donor prior to the interview or following blood donation are not significant steps requiring the maintenance of records. However, any aspect of the donor interview concerning his suitability and the phlebotomy is a significant step requiring the maintenance of records, signed or initialed by person(s) who actually per-

formed the work. The Commissioner recognizes that supervisors may have ultimate responsibility for the performance of their staff. Nevertheless, employees having direct responsibility for any significant step may need to be identified if deficiencies and substandard practices are to be expeditiously corrected. Accordingly the Commissioner accepts the comments requesting clarification of significant steps and a new Proposed § 606.160 (b) has been added to the regulation to specifically identify the records that must be maintained.

64. Several comments requested guidance concerning recordkeeping methods and requirements generally. In conjunction with this section of the regulation, the Commissioner will publish a proposal concerning the tabulation of recorded data in order to promote meaningful review and monitoring by the blood establishment and to facilitate a scheduled annual survey of all blood establishments by FDA.

65. Five comments concerning proposed § 606.160(c) (redesignated as § 606.160(d)) indicated that it is unrealistic to require that records of processing Source Plasma (Human) be retained for 6 months after the expiration date of the final product manufactured from the Source Plasma (Human). The comments noted that Source Plasma (Human) is normally sold to another establishment for further manufacture. Consequently, the Source Plasma (Human) supplier has no way of knowing the latest expiration date of the final product. One comment suggested it would be more practical to require that the supplier retain the records indefinitely, while two other comments suggested 5 years.

The Commissioner recognizes that it may be impractical, or perhaps impossible, for the supplier of Source Plasma (Human) to know the latest expiration date of a final product processed by another establishment. Consequently, it is also impractical to require that the supplier retain records of processing for 6 months after the latest expiration date for the final product that was manufactured from the source plasma. For this reason, the Commissioner intends to publish, at another time, a notice of proposed rule making to prescribe an expiration date for Source Plasma (Human). Interested persons will be given an opportunity for comment. The Commissioner has determined that in the interim, records of products having no expiration dates shall be retained indefinitely to facilitate the reporting of any unfavorable clinical reactions. Accordingly, § 606.160 has been amended in paragraph (e) to require that records be retained indefinitely when the product has no expiration date.

66. Three comments concerning proposed § 606.160(d) (redesignated § 606.160(e)) asked whether the regulation required that establishments maintain a separate list of unsuitable donors or permitted the flagging of individual donor records. One comment further asked whether the record of unsuitable donors must include the names of donors who are only temporarily unsuitable. Another

comment indicated that it is impractical to carry a complete list of unsuitable donors on mobile operations.

The Commissioner intended that the major impact of the regulation was to preclude from the marketplace, blood or blood products obtained from an unsuitable donor. The Commissioner advises that each blood establishment may develop its own system of recordkeeping to effectively identify unsuitable donors. Accordingly, the regulation does not prescribe a special system of recordkeeping. Rather, any record system used by a blood establishment must facilitate the identification of an unsuitable donor. The Commissioner agrees that it may be impractical, on a mobile operation, to carry a complete list of unsuitable donors. Therefore, upon return of the mobile unit to the blood establishment, donor records must be reviewed and action taken to assure that blood collected from an unsuitable donor will not be distributed. Accordingly, the Commissioner has amended the regulation to emphasize that records must be available so that products from unsuitable donors will not be distributed.

DISTRIBUTION AND RECEIPT; PROCEDURES AND RECORDS

67. One comment concerning proposed § 606.165 argued that unnecessary paperwork would be required if every unit of blood issued by a central blood bank must contain the name and address of the hospital. Another comment suggested that there is little need to specify on each distribution record the address of a consignee who is frequently supplied with the product. The comment suggested that the addresses of such consignees are always easily available at the blood establishment.

The Commissioner advises that the regulation does not require each unit of blood to have on its container the name and address of the hospital to which the unit is being sent. Rather, it requires that such information be in the distribution record of the blood establishment shipping the blood. The Commissioner agrees with the comment that the address of a consignee on each distribution record may not be needed if such information is easily available elsewhere in the blood establishment records in a form that will readily facilitate recall of a product. Accordingly, the regulation has been amended to require that distribution records contain information to facilitate the rapid identification of the name and address of the consignee.

68. In the original notice, the Commissioner proposed to require the maintenance of records for "each significant step" in the manufacture of blood products. It was the Commissioner's intent that records of receipt of blood and blood components be included since a system of recordkeeping of such data is essential to assure the identities and permit recall, if necessary, of each unit of blood. Indeed, almost all establishments receiving blood products recognize the importance of maintaining such records and currently do so. The Commissioner has con-

cluded that to promote specificity, the regulation should explicitly require such a system of recordkeeping and that such requirement be set forth in the new § 606.165 along with similar requirements applicable to distribution. Accordingly, that section has been amended to include requirements for receipt of blood and blood components in order to facilitate recall of blood products. In order to clarify any possible misapprehension that may have occurred concerning the scope of the proposal regarding records for receipt, the Commissioner will consider additional comments concerning this aspect of the regulation within the next 30 days, and such comments may justify further modification of this provision.

ADVERSE REACTION FILE

69. Twenty-three comments concerned proposed § 606.170 dealing with adverse reaction files. The comments posed general questions concerning the intended objectives of the proposed regulation. Almost all comments requested that the term "severe adverse reaction" be defined.

The Commissioner advises that the objective of the regulation is to reduce the possibility of adverse reactions by (a) determining the cause of the reaction; and (b) providing safeguards that eliminate, where possible, the causes leading to an adverse reaction. To achieve this objective, the technical staff of each transfusion facility must be informed of all transfusion reactions so that data may be made available to a physician to confirm suspected causes, including sequelae, such as antibody development that might require further blood usage demanding special technical handling, and to review and evaluate the adequacy of laboratory methods. For these reasons, transfusion reactions must be reported to the laboratory and records maintained there, in addition to any notes that may be inserted in the Patient's chart. Additionally, the collecting facility must be informed of all transfusion reactions when the reaction is attributed to a defect in the product obtained from the collecting facility. Accordingly, the regulation has been revised in § 606.170 to require clearly that (a) records be kept concerning any adverse reaction to the donor or recipient, (b) reports of each reaction be investigated, (c) transfusion reaction reports be communicated to and retained by the collecting facility when the reaction is attributed to a defect in the product, and (d) the Director, Bureau of Biologics, be informed of any deaths implicating a blood donation or transfusion as the cause.

The Commissioner uses the term "severe adverse reaction" to mean a fatal reaction. The Director, Bureau of Biologics, must be notified by telephone or telegraph as soon as possible when a blood donation or transfusion has been found to cause death, and a written report of the investigation must be submitted to the Director, Bureau of Biologics, within 7 days after the fatality.

Under the Administrative Procedure Act (5.U.S.C. 533 (b) and (d)), the Commissioner concludes that notice, public procedure and delayed effective date are unnecessary for the promulgation of § 606.170 as it does not impose an additional duty or burden on any person but rather relieves a restriction concerning plateletpheresis consistent with these good manufacturing practice regulations. Comments are nevertheless requested within the next 30 days and may justify further modification of this provision.

Therefore, under provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 501, 502, 510, 701, 52 Stat. 1040-1042 as amended, 1049-1050 as amended by 76 Stat. 780, 1055-1056 as amended, 76 Stat. 794 as amended, and sec. 301 of Pub. L. 87-781 (21 U.S.C. 321, 351, 352, 360 and note, 371), the Public Health Service Act (secs. 351 and 361, 58 Stat. 702 and 703 as amended (42 U.S.C. 262 and 264)), and the Administrative Procedure Act (secs. 4 and 10, 60 Stat. 238 and 243, as amended (5 U.S.C. 553, 702, 703, 704)) and under authority delegated to the Commissioner (21 CFR 2.120), Chapter I of Title 21 of the Code of Federal Regulation is amended in Subchapter F as follows:

1. By adding a new Part 606 to read as follows:

	Subpart A--General Provisions
Sec. 606.3	Definitions.
	Subpart B - Organization and Personnel
606.20	Personnel.
	Subpart C-Plant and Facilities
606.40	Facilities
	Subpart D-Equipment
606.60	Equipment
606.65	Supplies and reagents.
	Subpart E - [Reserved]
	Subpart F-Production and Process Controls
606.100	Standard operating procedures.
606.110	Plateletpheresis, leukapheresis and plasmapheresis.
	Subpart G-Finished Product Control
606.120	Labeling.
	Subpart H-laboratory Controls
606.140	Laboratory controls.
606.151	Compatibility testing.
	Subpart I-Records and Reports
606.160	Records.
606.165	Distribution and receipt: procedures and records.
606.170	Adverse reaction file.

AUTHORITY: Secs. 201, 501, 502, 510, 701, 52 Stat. 1040-1042 as amended, 1049-1051 as amended by 76 Stat. 780, 1055-1056 as amended, 76 Stat. 794 as amended, and sec. 301 of Pub. L. 87-781 (21 U.S.C. 321, 351, 352, 360 and note, 371), the Public Health Service Act (secs. 351 and 361, 58 Stat. 702 and 703 as amended (42 U.S.C. 262 and 264)), and the Administrative Procedure Act (secs. 4 and 10, 60 Stat. 238 and 243, as amended (5 U.S.C. 553, 702, 703, 704)).

Subpart A - General Provisions

§ 606.3 -Definitions.

As used in this part:

(a) "Blood" whole blood collected from a single donor and processed

either for transfusion or further manufacturing.

(b) "Unit" means the volume of blood or one of its components in a suitable volume of anticoagulant obtained from a single collection of blood from one donor.

(c) "Component" means that part of a single-donor unit of blood separated by physical or mechanical means.

(d) "Plasma for further manufacturing" means that liquid portion of blood separated and used as material to prepare another product.

(e) "Plasmapheresis" means the procedure in which blood is removed from the donor, the plasma is separated from the formed elements and at least the red blood cells are returned to the donor. This process may be immediately repeated once.

(f) "Plateletpheresis" means the procedure in which blood is removed from the donor, a platelet concentrate is separated, and the remaining formed elements and residual plasma are returned to the donor.

(g) "Leukapheresis" means the procedure in which blood is removed from the donor, a leukocyte concentrate is separated, and the remaining formed elements and residual plasma are returned

(h) "Facilities" means any area used for the collection, collection, compatibility testing, storage or distribution of blood and blood components.

(i) "Processing" means any procedure employed after collection and before compatibility testing of blood and includes the identification of a unit of donor blood, the preparation of components from such unit of donor blood, serological testing, labeling and associated recordkeeping.

(j) "Compatibility testing" means the in vitro serological tests performed on donor and recipient blood samples to establish the serological matching of a donor's blood or blood components with that of a potential recipient.

Subpart B - Organization and Personnel

§606.20 Personnel.

(a) A blood establishment shall be under the direction of a designated, qualified person who shall exercise control of the establishment in all matters relating to compliance with the provisions of this subchapter. This person shall also have the authority to represent the establishment in all pertinent matters with the Bureau of Biologics and to enforce, or direct the enforcement of, discipline and the performance of assigned functions by employees engaged in the collection, processing, compatibility testing, storage and distribution of blood and blood components. The designated director shall have an understanding of the scientific principles and techniques involved in the manufacture of blood products and shall have the responsibility for ensuring that employees are adequately trained in standard op-

erating procedures and that they are aware of the application of the pertinent provisions of this chapter to their respective functions.

(b) The personnel responsible for the collection, processing, compatibility testing, storage or distribution of blood or blood components shall be adequate in number, educational background, training and experience, including professional training necessary, combination thereof, to assure competent performance of their assigned functions, and to ensure that the final product has the safety, purity, potency, identity and effectiveness it purports or is represented to possess. All personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the procedures or control operations they perform, the necessary training or experience, and adequate information concerning the application of pertinent provisions of this part to their respective functions.

(c) Persons whose presence can adversely affect the safety and purity of the products shall be excluded from areas where the collection, processing, compatibility testing, storage or distribution of blood or blood components is conducted.

Subpart C-Plant and Facilities

§ 606.40 Facilities.

Facilities shall be maintained in a clean and orderly manner, and shall be of suitable size, construction and location to facilitate adequate cleaning, maintenance and proper operations. The facilities shall:

(a) Provide adequate space for the following when applicable:

(1) Private and accurate examinations of individuals to determine their suitability as blood donors.

(2) The withdrawal of blood from donors with minimal risk of contamination, or exposure to activities and equipment unrelated to blood collection.

(3) The storage of blood or blood components pending completion of tests.

(4) The quarantine storage of blood or blood components in a designated location pending repetition of those tests that initially gave questionable serological results.

(5) The storage of finished products prior to distribution.

(6) The quarantine storage, handling and disposition of products and reagents not suitable for use.

(7) The orderly collection, processing, compatibility testing, storage and distribution of blood and blood components to prevent contamination.

(8) The adequate and proper performance of all steps in plasma-pheresis, plateletpheresis and leukapheresis procedures.

(9) The orderly conduction of all packaging, labeling and other finishing operations.

(b) Provide adequate lighting, ventilation and screening of open windows and doors.

(c) Provide adequate, clean, and convenient handwashing facilities for personnel, and adequate, clean, and convenient toilet facilities for donors and personnel. Drains shall be of adequate size and, where connected directly to a sewer, shall be equipped with traps to prevent back-siphonage.

(d) Provide for safe and sanitary disposal for the following:

(1) Trash and items used during the collection, processing and compatibility testing of blood and blood components.

(2) Blood and blood components not suitable for use or distribution.

Subpart D-Equipment

§ 606.60 Equipment

(a) Equipment used in the collection, processing, compatibility testing, storage and distribution of blood and blood components shall be maintained in a clean and orderly manner and located so as to facilitate cleaning and maintenance. The equipment shall be observed, standardized and calibrated on a regularly scheduled basis as prescribed in the Standard Operating Procedures Manual and shall perform in the manner for which it was designed so as to assure compliance with the official requirements prescribed in this chapter for blood and blood products.

(b) Equipment that shall be observed, standardized and calibrated with at least the following frequency, include but are not limited to:

Equipment	Performance check	Frequency	Frequency of calibration
Temperature recorder	Compare against thermometer	Daily	As necessary.
Refrigerated centrifuge	Observe speed and temperature	Each day of use	Do.
Hematocrit centrifuge	Standardize with control preparation	do	Do.
General lab centrifuge			Tachometer every 6 mo.
Automated blood-typing machine	Observe controls for correct results	Each day of use	
Hemoglobinometer	Standardize against cyanmethemoglobin standard	do	
Refractometer	Standardize against distilled water	do	
Blood container scale	Standardize against container of known weight	do	As necessary.
Water bath	Observe temperature	do	Do.
Rh view box	do	do	Do.
Autoclave	do	do	Do.
Serologic rotators	Observe controls for correct results	do	As needed as necessary.
Laboratory thermometers			Before initial use.
Kinetic thermometers			Monthly.
Vacuum blood agitator	Standardize against container of known mass or volume	Each day of use	As necessary.

(c) Equipment employed in the sterilization of materials used in blood collection for disposition of contaminated products shall be designed, maintained and utilized to ensure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 131.5° C (251° F) maintained for 30 minutes by saturated steam at a pressure of 15 atmospheres or by an attained temperature of 170° C (338° F) maintained for 2 hours with dry heat.

§ 606.65 Supplies and reagents.

All supplies and reagents used in the collection, processing, compatibility testing, storage and distribution of blood and blood components shall be stored in a safe, sanitary and orderly manner.

(a) All surfaces coming in contact with blood and blood components intended for transfusion shall be sterile, pyrogen-free, and shall not interact with the product in such a manner as to have an adverse effect upon the safety, purity, potency or effectiveness of the product. All final containers and closures for blood and blood components not intended for transfusion shall be clean and free of surface solids and other contaminants.

(b) Each blood collecting container and its satellite container(s), if any, shall be examined visually for damage or evidence of contamination prior to its use and immediately after filling. Such examination shall include inspection for breakage of seals, when indicated, and abnormal discoloration. Where any defect is observed, the container shall not be used, or, if detected after filling, shall be properly discarded.

(c) Representative samples of each lot of the following reagents or solutions shall be tested on a regularly scheduled basis by methods described in the Standard Operating Procedures Manual to determine their capacity to perform as required

Reagent or solution	Frequency of testing
Antihuman serum	Each day of use.
Blood grouping serums	Do.
Lectins	Do.
Antibody screening and reverse grouping cells	Do.
Hepatitis test reagents	Each run.
Syphilis serology reagents	Do.
Enzymes	Each day of use.

(d) Supplies and reagents that do not bear an expiration date shall be stored in such a manner that the oldest is used first.

(e) Supplies and reagents shall be used in a manner consistent with instructions provided by the manufacturer.

(f) Items that are required to be sterile and come into contact with blood should be disposable whenever possible.

Subpart E - [Reserved]

Subpart F-Production and Process Controls

§ 606.100 Standard operating procedures.

(a) In all instances, except clinical investigations, standard operating procedures shall comply with published additional standards in Part 640 of this chapter for the products being processed: except that, references in Part 640 relating to licenses, licensed establishments and submission of material or data to approval by the Director, Bureau of Biologics, are not applicable to establishments not subject to licensure under section 351 of the Public Health Service Act.

(b) Written standard operating procedures shall be maintained and shall include all steps to be followed in the collection, processing, compatibility testing, storage and distribution of blood and blood components for homologous transfusion autologous transfusion and further manufacturing purposes. Such procedures shall be available to the personnel for use in the areas where the procedures are performed, unless this is impractical. The written standard operating procedures shall include, but are not limited to, descriptions of the following, when applicable:

(1) Criteria used to determine donor suitability, including acceptable medical history criteria.

(2) Methods of performing donor qualifying tests and measurements, including minimum and maximum values for a test or procedure when a factor in determining acceptability.

(3) Solutions and methods used to prepare the site of phlebotomy to give maximum assurance of a sterile container of blood.

(4) Method of accurately relating the product(s) to the donor.

(5) Blood collection procedure, including in-process precautions taken to measure accurately the quantity of blood removed from the donor.

(6) Methods of component preparation, including any time restrictions for specific steps in processing.

(7) All tests and repeat tests performed on blood and blood components during processing, including testing for hepatitis B surface antigen as prescribed in § 610.40 of this chapter.

(8) Pretransfusion testing, where applicable, including precautions to be taken to identify accurately the recipient blood samples and cross-matched donor units.

(9) Procedures for investigating adverse donor and recipient reactions.

(10) Storage temperatures and methods of controlling storage temperatures for all blood products and reagents as prescribed in §§ 600.15 and 610.53 of this chapter.

(11) Length of expiration dates, if any, assigned for all final products as prescribed in § 610.53 of this chapter.

(12) Criteria for determining whether returned blood is suitable for reissue.

(13) Procedures used for relating a unit of blood or blood component from the donor to its final disposition.

(14) Quality control procedures for supplies and reagents employed in blood collection, processing and pretransfusion testing.

(15) Schedules and procedures for equipment maintenance and calibration.

(16) Labeling procedures including safeguards to avoid labeling mixups.

(17) Procedures of plasmapheresis, plateletpheresis, and leukapheresis, performed, including precautions to be taken to ensure reinfusion of a donor's own cells.

(18) Procedure for preparing recovered (salvaged) plasma, if performed including details of separation, pooling, labeling, storage and distribution.

(c) All records pertinent to the lot or unit maintained pursuant to these regulations shall be reviewed before the release or distribution of a lot or unit of final product. The review or portions of the review may be performed at appropriate periods during or after blood collecting, processing, compatibility testing and storing. A thorough investigation, including the conclusions and follow-up of any unexplained discrepancy or the failure of a lot or unit to meet any of its specifications shall be made and recorded.

(d) In addition to the requirements of this subpart and in conformity with this section, any facility may utilize current standard operating procedures such as the manuals of the following organizations, as long as such specific procedures are consistent with, and at least as stringent as, the requirements contained in this part.

(1) American Association of Blood Banks.

(2) American National Red Cross.

(3) Other organizations or individual blood banks, subject to approval by the Director, Bureau of Biologics.

§ 606.110 Plateletpheresis, leukapheresis, and plasmapheresis.

(a) The use of plateletpheresis and leukapheresis procedures to obtain a product for a specific recipient may bear variance with the additional standards for specific products prescribed in this part provided that: (1) A physician has determined that the recipient must be transfused with the leukocytes or platelets from a specific donor, and (2) the procedure is performed under the supervision of a qualified licensed physician who is aware of the health status of the donor, and the physician has certified in writing that the donor's health permits plateletpheresis or leukapheresis.

(b) Plasmapheresis of donors who do not meet the donor requirements of §§ 640.63, 640.64 and 640.65 of this chapter for the collection of plasma containing rare antibodies shall be permitted only with the prior approval of the Director, Bureau of Biologics.

Subpart G-Finished Product Control

§ 606.120 Labeling

Labeling operations shall be separated physically or spatially from other operations in a manner adequate to prevent mixups.

(a) The labeling operation shall include the following labeling controls:

(1) Labels shall be held upon receipt pending review and proofing against all approved final copy, to assure accuracy regarding identity, content and conformity with the approved copy.

(2) Each type of label representing different products shall be stored and main-

tained in a manner to prevent mixups and stocks of obsolete labels shall be destroyed.

(3) All necessary checks in labeling procedures shall be utilized to prevent errors in translating test results to container labels.

(b) All labeling shall be clear and legible. The label provided by the collecting facility and the initial processing facility shall not be removed, altered or obscured, except that the label may be altered to indicate the proper name and other required labeling information for the contents remaining in a container after blood components have been removed. The container label shall include the following information as well as other specialized information, as required in this part or in Part 640 of this chapter for specific products:

(1) The proper name of the product placed in a prominent position.

(2) The name and address of the manufacturer, and if licensed, the license number.

(3) The donor or lot number relating the unit to the donor.

The expiration date, including the day and year, and if it is a factor, the hour, or in the case of plasma for further manufacture, the date of collection

(5) Essential instructions or precautions for use, including a warning that the Product may transmit the agent of hepatitis.

(6) Recommended storage temperature.

(7) Reference to an instruction circular that shall be available for distribution containing dosage information, adequate directions for use, route of administration, contraindications and other directions if product is not intended for further manufacturing.

(8) Quantity of product in container, which shall be accurate within ± 10 percent, except that the quantity of Cryoprecipitate Antihemophilic Factor (Human) need not be stated on the label and except that this provision shall not apply to Source Plasma (Human).

(9) Quantity of source material, and the kind and quantity of anticoagulant.

(10) Additives and cryoprotective agents added to the product that may still be present.

(11) Results of all tests performed when necessary for safe and effective use.

(12) The statement: "Caution: For Manufacturing Use Only" where applicable.

(13) The immunizing antigen used or the antibody present for products for further manufacturing, when applicable.

Subpart H - Laboratory Controls

§ 606.140 Laboratory controls.

Laboratory control procedures shall include:

(a) The establishment of scientifically sound and appropriate specifications, standards and test procedures to assure that blood and blood components are safe, pure potent and effective.

(b) Adequate provisions for monitoring the reliability, accuracy/precision

and performance of laboratory test procedures and instruments.

(c) Adequate identification and handling of all test samples so that they are accurately related to the specific unit of product being tested or to its donor, or to the specific recipient, where applicable.

§ 606.151 Compatibility testing.

Standard operating procedures for compatibility testing shall include the following:

(a) A method of collecting and identifying the blood samples of recipients to ensure positive identification.

(b) The use of fresh recipient serum samples less than 48 hours old for all pretransfusion testing.

(c) The testing of the donor's cells with the recipient's serum (major crossmatch) by a method that will demonstrate agglutinating, coating and hemolytic antibodies, which shall include the antiglobulin method.

(d) A provision that, if the unit of donor's blood has not been screened by a method that will demonstrate agglutinating, coating and hemolytic antibodies, the recipient's cells shall be tested with the donor's serum (minor crossmatch) by a method that will demonstrate

(e) Procedures to expedite transfusions in life-threatening emergencies. Records of all such incidents shall be maintained, including complete documentation justifying the emergency action, which shall be signed by the physician requesting the procedure.

Subpart I - Records and Reports

§ 606.160 Records.

(a) (1) Records shall be maintained concurrently with the performance of each significant step in the collection, processing, compatibility testing, storage and distribution of each unit of blood and blood components so that all steps can be clearly traced. All records shall be legible and indelible, and shall identify the person performing the work, include dates of the various entries, show test results as well as the interpretation of the results, show the expiration date assigned to specific products, and be as detailed as necessary to provide a complete history of the work performed.

(2) Appropriate records shall be available from which to determine lot numbers of supplies and reagents used for specific lots or units of the final product.

(b) Records shall be maintained that include, but are not limited to, the following when applicable:

(1) Donor records:

(i) Donor selection, including medical interview and examination and where applicable, informed consent.

(ii) Permanent and temporary deferrals for health reasons including reason(s) for deferral.

(iii) Donor adverse reaction complaints and reports, including results of all investigations and followup.

(iv) Therapeutic bleedings. Including signed requests from attending physi-

clans, the donor's disease and disposition of units.

(v) Immunization, including informed consent identification of the antigen, dosage and route of administration

(vi) Blood collection, including identification of the phlebotomist.

(2) Processing records:

(i) Blood processing, including results and interpretation of all tests and retests.

(ii) Component preparation, including all relevant dates and times.

(iii) Separation and pooling of recovered plasma.

(iv) Centrifugation and pooling of source plasma.

(v) Labeling, including initials of person(s) responsible.

(3) Storage and distribution records:

(i) Distribution and disposition, as appropriate, of blood and blood products.

(ii) Visual inspection of whole blood and red blood cells during storage and immediately before distribution.

(iii) Storage temperature, including initialed temperature recorder charts.

(iv) Reissue, including records of Proper temperature maintenance.

(v) Emergency release of blood, including signature of requesting physician obtained before or after release.

(4) Compatibility test records:

(i) Results of all compatibility tests, including crossmatching, testing of patient samples, antibody screening and identification.

(ii) Results of confirmatory testing.

(5) Quality control records:

(i) Calibration and standardization of equipment.

(ii) Performance checks of equipment and reagents.

(iii) Periodic check on sterile technique.

(iv) Periodic tests of capacity of shipping containers to maintain proper temperature in transit.

(v) Proficiency test results.

(6) Transfusion reaction reports and complaints, including records of investigations and followup.

(7) General records:

(i) Sterilization of supplies and reagents prepared within the facility, including date, time interval, temperature and mode.

(ii) Responsible personnel.

(iii) Errors and accidents.

(iv) Maintenance records for equipment and general physical plant.

(v) Supplies and reagents, including name of manufacturer or supplier, lot numbers, expiration date and date of receipt.

(vi) Disposition of rejected supplies and reagents used in the collection, processing and compatibility testing of blood and blood components.

(c) A donor number shall be assigned to each accepted donor, which relates the unit of blood collected to that donor, to his medical record, to any component or blood product from that donor's unit of blood, and to all records describing the history and ultimate disposition of these products.

(d) Records shall be retained for such interval beyond the expiration date for

the blood or blood components necessary to facilitate the reporting of any unfavorable clinical reactions. The retention period shall be no less than 5 years after the records of processing have been completed or 6 months after the latest expiration date for the individual product, whichever is a later date. When there is no expiration date, records shall be retained indefinitely.

(c) A record shall be available from which unsuitable donors may be identified so that products from such individuals will not be distributed.

§ 606.165 Distribution and receipt: procedures and records.

(a) Distribution and receipt procedures shall include a system by which the distribution or receipt of each unit can be readily determined to facilitate its recall, if necessary.

(b) Distribution records shall contain information to readily facilitate the identification of the name and address of the consignee, the date and quantity delivered, the lot number of the unit(s), the date of expiration or the date of collection, whichever is applicable, or for crossmatched blood and blood components, the name of the recipient.

(c) Receipt records shall contain the name and address of the collecting facility, date received, donor, or lot number assigned by the collecting facility and

the date of expiration or the date of collection, whichever is applicable.

§ 606.170 Adverse reaction file

(a) Records shall be maintained of any reports of complaints of adverse reactions regarding each unit of blood or blood product arising as a result of blood collection or transfusion. A thorough investigation of each reported adverse reaction shall be made. A written report of the investigation of adverse reactions including conclusions and followup, shall be prepared and maintained as part of the record for that lot or unit of final product by the collecting or transfusing facility. When it is determined that the product was at fault in causing a transfusion reaction, copies of all such written reports shall be forwarded to and maintained by the manufacturer or collecting facility.

(b) When a complication of blood collection or transfusion is confirmed to be fatal, the Director, Bureau of Biologics, shall be notified by telephone or telegraph as soon as possible; a written report of the investigation shall be submitted to the Director, Bureau of Biologics, within 7 days after the fatality by the collecting facility in the event of a donor reaction, or by the facility that performed the compatibility tests in the event of a transfusion reaction.

2. In Part 640 by adding a new § 640.27 to Subpart C to read as follows:

§ 610.27 Emergency provisions.

The USC of the plateletpheresis procedure to obtain a product for a specific recipient may be at variance with §§ 640.21(c) and 640.22(c) Provided, that (a) A licensed physician has determined that the recipient must be transfused with the platelets from a specific donor, and (b) The plateletpheresis procedure is performed under the supervision of a qualified licensed physician who is aware of the health status of the donor and the physician has certified in writing that the donor's health permits plateletpheresis.

Effective date. This regulation shall be effective December 18, 1975.

(Secs. 201, 501, 502, 610, 701, 62 Stat. 1040-1042 as amended, 1049-1051 as amended by 76 Stat. 780, 1055-1056 as amended, 76 Stat. 794 as amended, sec. 301 of Pub. L. 87-781 (21 U.S.C. 1351, 1352, 360 and note, 371), the Public Health Service Act (secs. 351 and 361, 68 Stat. 702 and 703 amended (42 U.S.C. 262 and 264)) and the Administrative Procedure Act (secs. 4 and 10, 60 Stat. 238 and 243, as amended (6 USC. 653, 702, 703, 704).)

Dated: November 11, 1975. . .

**SAM D. FINE,
Associate Commissioner
for Compliance.**

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