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Guidance for Industry

Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
August 2001

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GUIDANCE FOR INDUSTRY

Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture

This guidance document represents FDA's current thinking on changes to an approved application for all licensed human blood and blood components intended for transfusion or for further manufacture. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

INTRODUCTION

Frequently, a licensed biological product manufacturer determines that it is appropriate to make a change in the product, labeling, production process, quality controls, equipment, or facilities as documented in its approved license application(s). Section 601.12 of Title 21, Code of Federal Regulations (21 CFR 601.12) prescribes the requirements for you, the licensed biological product manufacturer, to report such changes for your licensed biological products to the Food and Drug Administration (FDA). This regulation only applies to the manufacture and distribution of licensed products. It does not apply to unlicensed products manufactured at unlicensed, registered-only facilities.

Under 21 CFR 601.12, you must report a change in the approved product, labeling, production process, quality controls, equipment, or facilities to FDA. You may report the change in: 1) a supplement requiring approval prior to distribution; 2) a supplement submitted at least 30 days prior to distribution of the product made using the change; or 3) an annual report, depending on its potential to have an adverse effect on the "identity, strength, quality, purity, or potency of the biological product as they may relate to the safety or effectiveness of the product" (Ref. 1) (referred to as "the safety or effectiveness of the product"). Before distributing a licensed product manufactured using a change, you are required to demonstrate, through appropriate validation and/or clinical or non-clinical laboratory studies, the lack of adverse effect of the change on the safety or effectiveness of the product.

The three reporting categories for changes to an approved application are defined in 21 CFR 601.12:

1) Changes that have a substantial potential to have an adverse effect on the safety or effectiveness of the product, that require submission of a supplement and approval by FDA prior to distribution of the product made using the change (major changes);

2) Changes that have a moderate potential to have an adverse effect on the safety or effectiveness of the product, that require submission of a supplement to FDA at least 30 days prior to distribution of the product made using the change or, for some changes, the 30 days may be waived (moderate changes); and

3) Changes that have minimal potential to have an adverse effect on the safety or effectiveness of the product, that are to be described by the applicant in an annual report (minor changes).

We, the Center for Biologics Evaluation and Research (CBER), have developed this guidance in response to public comments on the July 1997, Guidance for Industry - Changes to an Approved Application: Biological Products (Ref. 2), and on the CBER Biologics Workshop on December 2, 1997, discussing the Biologics License Application (BLA) and the reporting requirements for changes to an approved application for manufacturers of licensed Whole Blood and Blood Components intended for transfusion and for further manufacture (Ref. 3). This guidance applies to the manufacture of all licensed Whole Blood and blood components, Source Plasma, and Source Leukocytes intended for transfusion and for further manufacture into both injectable and non-injectable products. It is intended to assist you in determining which reporting mechanism is appropriate for a change to an approved license application. It replaces the recommendations in the Guidance for Industry: Changes to an Approved Application: Biological Products, July 1997, for the above mentioned products. This guidance also revises and finalizes the draft guidance entitled "Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture," that was announced in the Federal Register of January 3, 2000 (65 FR 134).

If you make a change to an approved license application, you must also conform to other applicable laws and regulations, including the current good manufacturing practice (cGMP) requirements of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) and regulations in 21 CFR parts 210, 211, and 600 through 680. For example, you must comply with recordkeeping requirements and ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection.

Under each section of the guidance document, we provide categories of changes to be reported under 21 CFR 601.12. The guidance also provides lists of changes that we currently believe you may report under each category. The lists are not intended to be all-inclusive. We have moved some of the changes listed in a specific reporting category in the July 1997 guidance on reporting changes to an approved application for biological products to other reporting categories in this guidance. In this guidance, we describe the format for the annual report and

explain the comparability protocol. We have included a separate section on labeling, describing the labeling changes that you would submit as supplements requiring prior approval supplements submitted at the time the change is made, or to be included in the annual report. If you need further guidance, you should call the Division of Blood Applications at (301) – 827-3543.

Because we have replaced the individual establishment and product licenses with a single biologics license (Ref. 4), you may combine or bundle multiple changes into one submission. For example, you may report a change in the manufacture of one or more products at one or more manufacturing locations. For clarity, we request that bundling be limited to related changes. If the review of all items in a bundled submission cannot be completed at the same time, we will separate the items still under review from the items for which the review is complete and final action (e.g., approval) can go forward. We have published additional guidance describing the specific items that are to be included in a submission (Ref. 5).

You should prominently label each submission with the reporting category under which you are reporting your change, e.g., "Prior Approval Supplement", "Supplement - Changes Being Effected in 30 Days", "Supplement - Changes Being Effected" or "Annual Report." You should include a Form FDA 356h "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use" with each submission (Ref. 6). We encourage you to use a cover letter to introduce and summarize the supplement. For guidance in preparing a supplement, you may refer to the Guidance for Industry – For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use" (Ref. 5).

You should report changes to your approved establishment, product or biologics license applications to the Director, Center for Biologics Evaluation and Research, Office of Blood Research and Review, Division of Blood Applications, HFM-370, c/o Document Control Center (HFM-99), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448.

II. DEFINITIONS

Acquisition - the purchase of a facility previously operated by an applicant under one U.S. license number by an applicant holding a different U.S. license number or by a new applicant. The acquired facility will no longer be connected to the original U.S. license number. We will either revoke or modify the original license to delete the facility. The license application for the legal entity acquiring the facility will be supplemented to include the manufacture of product at the acquired facility. If a new applicant has acquired a facility, we will grant a new license. We previously referred to acquisitions as 'rollovers' (Ref. 7).

Applicant - any person or legal entity that has submitted an application to manufacture a product subject to licensure under section 351 of the Public Health Service Act (PHS Act). The applicant assumes responsibility for compliance with the applicable product and establishment standards and for Quality Assurance (QA) oversight of all manufacturing steps (Ref. 8). Also see **manufacturer.**

Application - request submitted by the applicant for a biologics license, including supportive documentation, in order to manufacture and distribute in interstate commerce, a product subject to licensure under section 351 of the PHS Act.

AR - Annual Report [21 CFR 601.12(d)].

Authorized Official - person(s) designated by the applicant to communicate with the FDA on behalf of the applicant. Authorized officials can initiate applications or supplements to a license application, discuss submissions with our representatives, provide additional information in support of the submissions, and withdraw applications or supplements (Ref. 9). The applicant or manufacturer should immediately notify us in writing if there is a change in the authorized official(s). We will acknowledge receipt of the notification.

Circular of Information - instruction circular that provides adequate directions for the use of blood products intended for transfusion. The circular contains descriptions of the blood products, information on the tests performed on the components, indications for use, contraindications, cautions and administration recommendations [21 CFR 606.122].

CBE – Changes being effected (30 days waived) [21 CFR 601.12(c)(5)].

CBE30 – Changes being effected in 30 days [21 CFR 601.12(c)].

Contractor - any person or entity, other than the applicant, that performs part or all of the manufacturing of the licensed product as a service to the applicant. The applicant assumes responsibility for the contractor's compliance with the applicable product and establishment standards. Both the applicant and the contractor are legally responsible for the work performed by the contractor (Ref. 10). All contractors performing a manufacturing step of a licensed product must be registered with FDA, unless they are exempt from registration [21 CFR part 607].

Contractual Agreement – agreement between a manufacturer and a contractor, that describes the manufacturing steps performed by the contractor. Although you do not need to include the specific legal contract in your submission, you should include a description of the services requested from all contractors performing a manufacturing step for you (e.g., outside testing laboratories performing routine donor/product testing and confirmatory testing, irradiation facilities, suppliers of red blood cells for immunization, and storage facilities). This should also be available for review during inspection.

CP – Comparability Protocol [21 CFR 601.12(e)].

Disease-Associated Antibody Donors - donors who meet all the required/recommended normal Source Plasma donor suitability criteria, except that their plasma contains pre-existing IgG antibodies as a result of previous exposure to certain diseases or cellular antigens (Ref. 11).

Disease-State/High-Risk Donors - donors whose plasma contains or lacks a specific property (e.g., protein, antibody, inherited trait) as a result of their disease. These donors may not meet all the required or recommended normal Source Plasma donor suitability criteria.

Establishment/Facility - includes any and all establishments used by the manufacturer for collection, processing, product testing, compatibility testing, storage, or distribution of licensed Whole Blood and blood components. Any facility in which a manufacturing step is performed must meet the specifications and procedures established in the biologics license application designed to insure the continued safety, purity and potency of the biological product [21 CFR 600.3(w)]. Establishment and facility have the same meaning (Ref. 4). For the purposes of this document, the facilities are separated into three categories determined by the manufacturing steps they perform: Major Facilities, Auxiliary Facilities and Transfusion Services (see Appendix D).

Major Facilities:

- **Collection Facility** – facility that collects Whole Blood and/or apheresis products, and/or performs infrequent plasmapheresis, but that does not perform FDA required or recommended blood and plasma donor testing or prepare components from Whole Blood. Collection facilities may also label, store, and distribute blood products.

- **Community Blood Bank** - commercial or non-profit blood collection/processing facility, not part of a hospital system, that may perform manual and/or automated blood collection, prepare components from Whole Blood, perform FDA required or recommended blood and plasma donor testing (including compatibility testing), and routinely labels, stores, and distributes blood and/or blood products to one or more hospitals. Community blood banks may also prepare irradiated, frozen, deglycerolized and/or leukoreduced products.

- **Component Preparation Facility** - intermediate processing facility that prepares components from Whole Blood collected at a mobile or fixed collection site but does not perform FDA required or recommended blood and plasma donor testing. Component preparation facilities may also perform automated collection of blood products, and/or label, store, and distribute blood products and/or may prepare irradiated, frozen, deglycerolized and/or leukoreduced products.

- **Hospital Blood Bank** - facility located within a hospital that routinely performs manual and/or automated blood collection and processes Whole Blood into components. A hospital blood bank may also prepare irradiated, frozen, deglycerolized and/or leukoreduced products, distribute blood products to other hospitals and may perform FDA required or recommended blood and plasma donor testing and compatibility testing.

- **Plasmapheresis Center -** facility licensed by CBER that collects Source Plasma by manual and/or automated methods for commercial distribution. Plasmapheresis centers may also perform FDA required or recommended blood and plasma donor testing.

- **Product Testing Laboratory** – facility that performs routine FDA required or recommended blood and plasma donor testing.

Auxiliary Facilities:

- **Distribution Center** - facility that stores blood or blood products under specific controlled conditions prior to shipment to the final user, including suppliers of source material for further manufacture, such as Recovered Plasma, Source Plasma, Whole Blood, Red Blood Cells, or Platelets for diagnostic product use; for example, Whole Blood facilities that intend to redistribute the product to transfusion centers, Source Plasma warehouses that intend to redistribute the product to fractionators or Recovered Plasma holding facilities or brokers intending to redistribute the product to diagnostic product manufacturers or fractionators. This term does not include transfusion services that occasionally ship excess products as a means to manage the blood supply in a specific region or during a rare emergency because their products are not being stored with the intent to distribute.

- **Donor Center** - facility that only performs manual collection of Whole Blood and does not collect blood product by automated methods, prepare blood components or perform routine FDA required or recommended blood and plasma donor testing.

Transfusion Services:

- **Transfusion Service** – facility that performs compatibility testing for blood and blood components, but does not routinely collect blood, process Whole Blood into components (except Red Blood Cells and Recovered Plasma) and does not perform FDA required or recommended blood and plasma donor testing.

Fractionated Blood Derivatives - sterile solutions of a specific protein(s) derived from human blood, e.g., albumin, plasma protein fraction and immune globulin.

Inspection – an on-site evaluation conducted by FDA personnel of operations at a regulated establishment to assess whether it is in compliance with applicable laws and regulations and in conformance with the establishment's approved applications or the establishment's application for a U.S. license. FDA inspections may be conducted for several purposes.

- **Pre-Approval Inspection** – an announced or unannounced inspection conducted by CBER personnel and/or investigators from the Office of Regulatory Affairs (ORA). This inspection is conducted as part of the review of a supplement to an approved biologics license application. Examples of supplements that would require pre-approval inspections include submissions for irradiated blood products, or implementation of a red blood cell immunization program under a Source Plasma license.

- **Pre-License Inspection** – an announced inspection conducted by a team of CBER and ORA personnel. This comprehensive inspection is conducted as part of the review of an application for a U.S. license, or a supplement to an approved biologics license application for a new facility or product. Examples of applications and supplements that would require pre-license inspections include a new blood establishment, or an additional major facility operating under an existing U.S. license.

- **Post-Approval Inspection** – a periodic unannounced inspection conducted by ORA investigators. This inspection is a surveillance activity, conducted to assess whether the operations of licensed and unlicensed blood establishments are in compliance with applicable laws and regulations and with commitments made in the approved license application (for licensed establishments). Examples of post-approval inspections include the annual/biennial inspections and directed inspections. Directed inspections are unannounced "for cause" inspections conducted by ORA investigators who audit selected operations of an establishment. Examples of directed inspections include a follow-up to a fatality investigation or consumer complaint.

Manufacturer - any person or legal entity engaged in the manufacture of a product subject to licensure under the PHS Act. Manufacturer also includes any person or legal entity that is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards [21 CFR 600.3(t)].

Manufacturer's Instructions – instructions for use of equipment, test kits, reagents, supplies, etc., used in the manufacture of Whole Blood and blood components that are prepared by the manufacturer of the equipment, test kits, reagents, supplies, etc. Manufacturer's instructions may be described in the equipment operator's manuals and reagents or supplies package inserts.

Manufacturing - all steps involved in the preparation of a product intended for transfusion or for further manufacture into injectable or non-injectable products. Manufacturing includes determining donor suitability, the informed consent and collection procedure, component preparation, product/donor testing (including quality control), labeling, storage of the product, compatibility testing, and the quarantine and destruction of unsuitable blood products [21 CFR 600.3(u) and 21 CFR 607.3(d)]. The steps may be performed by the manufacturer holding the biologics license or by a contractor who performs one or more of the manufacturing steps.

Merger - union of two or more licensed manufacturers to form a new legal entity. FDA will issue a new U.S. license number to the new entity.

PAS – Prior approval supplement [21 CFR 601.12(b)].

Source Material - blood component derived from human blood that is collected by either manual or automated apheresis techniques and is intended for further manufacturing into injectable or non-injectable products.

Supplement - written request submitted to the Director, Center for Biologics Evaluation and Research, to approve a change in an approved license application [21 CFR 600.3(gg)].

Transfusion Blood Components - blood components (Whole Blood, Red Blood Cells, Platelets, Plasma, Cryoprecipitate, or Granulocytes) derived from human blood collected by either manual whole blood collection or automated apheresis techniques and intended to be transfused to human recipients.

III. CHANGES UNDER 21 CFR 601.12(b) - Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes). [PAS]

Under 21 CFR 601.12(b), if you make any change to your product, production process, quality controls, facilities, or equipment, that has a substantial potential to have an adverse effect on the safety or effectiveness of the product, you must submit a supplement and receive our approval before distributing the product made using the change. For a change under this category, you must submit a supplement to your approved license application that includes the following:

- a detailed description of the proposed change;
- the products involved;
- the manufacturing site(s) or area(s) affected;
- a description of the methods used and studies performed to evaluate the effect of the change on the product's safety or effectiveness;
- the data derived from those studies;
- relevant validation protocols and data;

- appropriate labels; and
- relevant standard operating procedure(s) (SOP) or a list referencing previously approved relevant SOP.

You should submit any change in a facility or manufacturing process in the prior approval category unless specified in this guidance that it may be reported in another category.

We consider the following types of changes to be major changes, for which submission and approval of a supplement prior to distribution of product made using the change must occur:

A. Product Manufacturing/Procedural Changes

1. Implementation of a new manufacturing process, to include but not be limited to:
    a. Leukocyte reduction;
    b. Irradiation;
    c. Freezing/deglycerolizing;
    d. Rejuvenating; and
    e. Washing.
2. Addition or revision of SOP for the following categories if the change is <u>less</u> restrictive than previously approved or is not addressed in published FDA guidance documents* (Ref. 7):
    a. Donor suitability, including donor deferral;
    b. Blood collection, including arm preparation;
    c. High risk behavior questions, including AIDS information;
    d. Donor history forms, including informed consent;
    e. Product manufacturing for licensed products; and
    f. Quarantine and disposition of unsuitable product.

    ***NOTES**:
    - Report changes in the content of the procedure or form. You do not need to report changes in format only and minor editorial changes to SOP and forms.
    - You may reference previously approved SOP and forms. You should include the FDA application or supplement tracking number when referencing a previously approved SOP or form.
    - You should submit to us for review SOP revisions in the above areas prepared in response to post-approval inspectional observations
3. Implementation of procedures and/or donor history forms that differ from and are less restrictive than the FDA-approved AABB Uniform Donor History Questionnaire, manufacturer's directions or recommendations described in FDA guidance documents. This includes a change in quality control procedures. If the modifications are more restrictive or if the procedure is performed following the manufacturer's directions, you may report the change in

the annual report. You may report the addition of procedures or tests that are not required or recommended by FDA in the annual report.

4. Use of an abbreviated donor history questionnaire for repeat or frequent donors.
5. Implementation of a computer-assisted donor history questionnaire where the computer system can be accessed from remote locations, is able to make decisions about donor suitability or is interfaced with other computer systems, either at the same collection center or at other facilities.
6. Change from manufacturing a sole product by automated apheresis to manufacturing additional products as by-products. Exception: Collection of plasma as a by-product to an approved plateletpheresis program should be reported as a CBE30 (see section IV.A.2.).
7. Request to manufacture additional products; e.g., Platelets Pheresis, Source Plasma or Source Leukocytes.
8. Addition of an immunization program for red blood cells or unlicensed vaccines.
9. Implementation of a physician substitute program in a Source Plasma facility (Ref. 12).
10. Collection of Source Plasma from disease-state or high-risk donors.
11. Request for approval of a comparability protocol.
12. Request for approval of an alternative procedure under 21 CFR 640.120 for which there is no published guidance.

B. Equipment Changes

1. Conversion from manual to automated collection of blood components; e.g., Platelets, Plasma (both Fresh Frozen and Source), Red Blood Cells, Source Leukocytes.
2. Changes or upgrades in automated apheresis equipment that affect the purity, potency or quality of the product(s). These changes include but are not limited to: increase in product yield; change in storage conditions; change in anticoagulant; leukocyte reduction; collection of an additional or different product, for example, a change from COBE LRS Version 5.1 to Turbo Version 7.
3. Change in manufacturer of automated apheresis equipment used in the collection of Red Blood Cells or Platelets, e.g., change from Haemonetics MCS to Cobe Trima.

C. Contractor Changes

1. Use of, or change to, a new facility or any facility not previously engaged in blood product testing as a contract testing laboratory to perform the routine serologic and infectious disease screening testing, and supplemental and/or

confirmatory testing for blood and blood products. These laboratories perform the tests of record (tests used to determine donor/product suitability).

2. Use of, or change in, a contractor that was not previously engaged in performing a manufacturing step on blood products, to perform the manufacturing step. This includes, but is not limited to, contractors who irradiate blood products or supply red blood cells for immunization.

D. Facility Changes

1. Expanding operations by adding a major facility where licensed products are manufactured. This includes the addition of a contractor to perform the manufacturing step.
    a. Major facilities where Red Blood Cells, Fresh Frozen Plasma, Platelets, and Platelets, Pheresis are collected using automated collection systems, Source Plasma and Source Leukocytes are collected using either manual or automated collection methods, or routine FDA required or recommended blood and plasma testing is performed.
    b. Acquisition of major facilities previously operating under another U.S. license number that will now manufacture product under the U.S. license number of the legal entity acquiring the facility.
2. Relocation of a major facility where product manufacturing is performed that results in a change in core center personnel, and/or a change in SOP or equipment. You should also report the relocation of any contractor that results in a change in personnel and/or a change in SOP or equipment.

IV. CHANGES UNDER 21 CFR 601.12(c) - Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change (moderate changes). [CBE30]

Under 21 CFR 601.12(c), if you make any change in your product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the safety or effectiveness of the product, you must submit a supplement to us at least 30 days prior to distribution of a licensed product made using the change. The requirements for the content of these supplements are the same as for PAS.

You must specify that the changes are being reported in this category by labeling the submission: "Supplement - Changes Being Effected in 30 Days." Within 30 days of the date we receive the submission, we will determine if the change or changes have been reported in the proper category and will notify you if they have not. If we have not notified you otherwise within 30 days after we receive the supplement, you may distribute your product under licensure, using the change described in your supplement. You do not have to wait for our written approval before distributing a product made using a change reported in this category. If we do not notify you, it

does not mean that we have approved the changes reported in your supplement, merely that you have reported the changes in the proper category. Our review of your submission will proceed after we have determined that the changes are reported in the proper category.

We will not notify you when we receive your CBE30 supplements; instead, we recommend that you have a mechanism to track the date we received the submission; e.g., a mail service that will return confirmation of the receipt date.

If we determine that the information submitted in your supplement fails to demonstrate the continued safety or effectiveness of the product made using the change, we will try to resolve the problems with you. In assessing your plans to correct the problem, we will consider your reasons for making the change and the available alternatives to the change. If we find that your product in distribution poses a danger to public health, or if we determine that there are unresolved issues, we may require that you cease distribution of the product made using the change or that you remove the product from distribution pending resolution of the issues related to the change.

We consider the following types of changes to be moderate changes, for which submission of a supplement at least 30 days prior to the distribution of the product made using the change should occur:

A. Product Manufacturing/Procedural Changes

1. Addition of the collection of plasma as a by-product in an approved plateletpheresis program, provided the applicant is otherwise approved to manufacture the plasma product.
2. Request to manufacture the following products:
    a. Plasma Cryoprecipitate-Reduced, provided the applicant is approved to manufacture Cryoprecipitated AHF and Fresh Frozen Plasma.
    b. Fresh Frozen Plasma Donor Retested, provided the applicant is approved to manufacture Fresh Frozen Plasma.
3. Implementation of an immunization program for licensed vaccines where the program is consistent with the vaccine insert instructions.
4. Implementation of a self-administered donor history questionnaire where the information is presented to the donor on a printed form that the donor must read or that is presented using audio/visual tools.
5. Implementation of a computer-assisted donor history questionnaire where the computer system operates as a stand-alone system, does not make decisions about donor suitability, and is not interfaced with other computer systems, either at the same collection center or at other facilities.
6. Request for an alternative procedure under 21 CFR 640.120 for which published guidance is available and implementation conforms with the guidance,

e.g., implementation of an infrequent plasmapheresis donor collection program that is consistent with FDA's guidance for this program.

7. Implementation of recommendations described in FDA guidance documents, if followed without modifications and directed to be reported in this manner by the guidance document.

B. Equipment Changes

1. Change in manufacturer of automated plasma apheresis equipment, e.g., change from Haemonetics PCS to Fenwal Autopheresis C.

C. Contractor Changes

1. Use of, or change to, an FDA registered contract testing laboratory, currently engaged in blood product testing, to perform the routine serologic and infectious disease screening testing, and supplemental and/or confirmatory testing for blood and blood products. These laboratories perform the tests of record (tests used to determine donor/product suitability).
2. Use of, or change to, an FDA registered contractor, currently engaged in performing manufacturing steps on blood products, to perform a specific manufacturing step, e.g., irradiation of blood products.
3. Use of an off-site contract storage facility to store unlicensed product collected under a pending license application or for the storage of excess licensed product that meets all product release criteria. The storage facility may also distribute licensed product to the final user.

D. Facility Changes

1. Change in legal name of the applicant. This will cause the issuance of a new license number.
2. Relocation of a major facility where product manufacturing is performed and there is no change in SOP, equipment, and core center personnel, especially center management and medical personnel. Report relocations of facilities that result in a change in core center personnel as a prior approval supplement.
    a. Include relocation of all contractors where there is no change in SOP, equipment, and core personnel.
    b. Do not include move of auxiliary facilities. You must report this submitting a revised Form FDA 2830 at the time of the move and by updating your organizational report in the annual report.

V. CHANGES UNDER 21 CFR 601.12(c)(5) - Changes requiring supplement submission prior to distribution of the product made using the change (30 days is waived). [CBE]

As described in 21 CFR 601.12(c)(5), we may determine that, based on our experience with a particular type of change, that the supplement for such change is usually complete and provides the proper information. Likewise, there may be particular assurances that the proposed change has been appropriately submitted, such as when the change has been validated in accordance with a previously approved protocol. In these circumstances, we may determine that the product made using the change may be distributed under licensure at the time we receive your supplement. We recommend that you have a mechanism to track the date we received your CBE submission.

You should specify that the changes are being reported in this category by labeling the submission: "Supplement - Changes Being Effected." We will determine if the change has been reported in the proper category and will notify you if it has not. You do not have to wait for our written approval before distributing a product made using a change in this category. If we do not notify you, it does not mean that we have approved the changes reported in your supplement, merely that you have reported the changes in the proper category. Our review of your submission will proceed after we have determined that the changes are reported in the proper category.

If we determine that the information submitted in your supplement fails to demonstrate the continued safety or effectiveness of the product made using the change, we will try to resolve the problems with you. In assessing your plans to correct the problem, we will consider your reasons for making the change and the available alternative to the change. If we find that your product in distribution poses a danger to public health, or if we determine that there are unresolved issues, we may require that you cease distribution of the product made using the change or that you remove the product from distribution pending resolution of the issues related to the change.

Under 21 CFR 601.12(c)(5) and based on our experience, we consider the following types of changes to be moderate changes that could be implemented, without a previously approved comparability protocol (see section VII), at the time we receive your supplement:

A. Product Manufacturing/Procedural Changes

1. Implementation of another manufacturer's previously approved SOP, with written permission from the manufacturer.
2. Implementation of recommendations described in final FDA guidance documents, if followed without modifications and directed to be reported in this manner by the guidance document.

B. Facility Changes

1. Voluntary revocation or permanent closure of a major facility. You may report closure of auxiliary facilities in the annual report.
2. Temporary move or closure and reopening of a major facility provided there are no changes in SOP, equipment, and core center personnel. You should indicate the estimated time for the change and describe the plans for restarting operations at the original site in your submission.

VI. CHANGES UNDER 21 CFR 601.12(d) - Changes to be described in an annual report (minor changes). [AR]

Under 21 CFR 601.12(d), you must document changes to the product, production process, quality controls, equipment, or facilities, that have minimal potential to have an adverse effect on the safety or effectiveness of the product in an annual report submitted within 60 days of the anniversary date of approval of your first product application in each year you have changes to report in this category. You must include a list of all licensed products involved, and a full description of the manufacturing and controls changes including: the manufacturing site(s) or area(s) involved, the date each change was made, and a cross-reference to relevant validation protocol(s) and/or approved SOP in your annual report.

On October 20, 1997, we sent a letter to all licensed blood and plasma establishments notifying them of the date of their first product application approval. The month and day of this date represents your annual report date. Minor changes to any and all licensed products must be reported in the annual report within 60 days of this date. You may request an alternate date, but you must make your request to us in writing. We will notify you if this date is acceptable. Once approved, this alternate date will become your new annual report date.

Annual reports should contain information about minor changes to any and all licensed products implemented since the prior annual report. Submit one original annual report and two copies to us for review. If there are no minor changes, you need not submit an annual report.

We will review the annual report to determine if the changes were reported in the proper category. If the annual report contains changes that should have been reported as supplements, we will notify you in writing and by telephone of those changes that should be submitted as supplements. In such cases, we will try to resolve problems with you concerning your annual report. If we find that your product in distribution poses a danger to public health, or if we determine that there are unresolved issues, we may require that you cease distribution of the product made using the change or that you remove the product from distribution pending resolution of the issues related to the change.

We consider the following types of changes to be minor changes, to be reported in an annual report:

A. Product Manufacturing/Procedural Changes

1. Revision of SOP for the following categories if the change is more restrictive than previously approved or is not described in published FDA guidance documents, e.g. deferring donors who are at risk for Lyme disease:
    a. Donor suitability, including donor deferral
    b. Blood collection, including arm preparation (if changing to an approved method and following manufacturer's instructions)
    c. High risk behavior questions, including AIDS information
    d. Donor history forms, including informed consent
    e. Product manufacturing for licensed products
    f. Quarantine and disposition of unsuitable product
2. Implementation of a program to collect Source Plasma from normal donors with pre-existing disease-associated, red blood cell and/or HLA antibodies in Source Plasma (Ref. 11).
3. Implementation of a FDA-approved AABB Uniform Donor History Questionnaire, if used without modifications or if modifications are more restrictive.
4. Implementation of recommendations described in final FDA guidance documents, if followed without modifications and directed to be reported in this manner by the guidance document.
5. Change in the quality control method if the procedure is consistent with the manufacturer's directions. This includes the methods used to quality control the systems involved in product manufacturing, e.g., blood products, equipment, reagents, supplies.
6. Implementation of additional procedures or tests which are not required or recommended by FDA. (If the test or procedure is included in the informed consent, the form should not contain any exculpatory language or claims about the procedure or test.)
7. Change in collection sets or leukocyte reduction filters for products prepared from Whole Blood, if used according to manufacturer's instructions.

B. Equipment Changes

1. Changes or upgrades by the device manufacturer of automated apheresis equipment that does not affect the purity, potency or quality of the product(s), if the facility is already approved for the original procedure, e.g., upgrade in plasmapheresis equipment from Haemonetics PCS to Haemonetics PCS2 or upgrade to Haemonetics PCS2 Version G to display red blood cell loss.
2. Change in irradiation equipment used by you or your contractor, e.g., from gamma irradiator to linear accelerator or to a different gamma irradiator manufacturer.
3. Implementation of a blood establishment computer system that maintains data used by blood establishment personnel to make decisions regarding the suitability of donors and the release of blood and blood components for transfusion or for further manufacture. Do not include the use of a computer-assisted donor history questionnaire. Report the name of the software manufacturer, name and version number of the software. You should include the following in the annual report:
    a. Installation of both commercially developed software and software developed and used in-house.
    b. Implementation of data entry and retrieval or library database systems.
    c. Change in blood establishment computer software manufacturers or software versions, provided there are no major changes in the processes performed by the computer (e.g., adding an electronic crossmatch function) or no modifications made by the user that changes the intended functionality of the new system.
    d. Implementation of a computer/electronic crossmatch.
4. Implementation of automated equipment to perform ABO/Rh, syphilis and infectious disease screening testing on donor blood samples.
5. Change in infectious disease screening testing methodology if the procedure is consistent with manufacturer's directions.
6. Change in equipment that performs total protein and serum/plasma protein electrophoresis on donor specimens.
7. Change in equipment that performs vital sign testing (e.g., pulse, blood pressure, temperature) and hemoglobin/hematocrit testing on blood donors or donor specimens.
8. Use of sterile connecting (docking) device to manipulate product in a sterile manner (e.g., take samples; attach transfer bag, needle, saline, anticoagulant or other processing solutions; prepare aliquots; pool products) if approved to manufacture the product and use of the device is consistent with manufacturer's directions.
9. Changes or upgrades in automated apheresis equipment that results in a decrease in donation time.

C. Contractor Changes

1. Use of, or change in, a contract testing laboratory that performs reference or quality control testing or tests that are not required or recommended by FDA. This does not include a change in a contract testing laboratory that performs the infectious disease tests of record. Such a change must be reported as a PAS or CBE30. (See sections III. C. 1. and IV. C. 1.)
2. Temporary use of a previously approved alternate or back-up contractor to perform a manufacturing step. Include the dates the alternate contractor was used. A permanent change in a contractor should be reported as a PAS or CBE30. (See sections III. C. 1. and IV. C. 1.)
3. Use of, or change in, a contractor to provide personnel responsible for collecting blood products or performing quality assurance activities.

D. Facility Changes

1. Addition or deletion of a self contained motorized vehicle used for blood and blood product collection.
2. Change in "doing business as" name that does not affect the legal entity name on the license.
3. Openings, moves and closures of auxiliary facilities operating under a U.S. license. You must send in a facility registration form (Form FDA 2830) within five days of an opening, move or closure of the center [21 CFR 607.21 and 607.26].

The following information should **not** be included in the annual report:

- Major or moderate changes that have received FDA approval as supplements during the reporting period, unless they are included in the organizational changes.
- Major or moderate changes submitted as supplements and currently under our review.
- Shipment of source blood, plasma or serum that is repeatedly reactive for an infectious disease marker and is to be used in the manufacture of vaccines and licensed or unlicensed in-vitro diagnostic biological products. You must still report these shipments in the manner stated in 21 CFR 610.40(d).
- Notification of the development of unexpected antibodies in donors participating in red blood cell immunization programs. You should keep this information available so that it may be reviewed during FDA inspections (Ref. 7). If the development of unexpected antibodies is due to an error in immunization practices, you must report this under 21 CFR 600.14.

- Biological product deviation (error and accident) or incident reports, fatalities and recalls. You must still notify CBER, Office of Compliance and Biologics Quality, of these events using the current reporting requirements [21 CFR 606.170].
- Validation data compiled during the installation and qualification of new or upgraded equipment, computer systems or software. You should keep this information available so that it may be reviewed during FDA inspections.
- You should report the following corporate changes to us at the time they occur:
    - Change in corporate mailing address of the legal entity.
    - Change in, or addition of, an authorized official.

Reporting Format for the Annual Report

We recommend that you use the following reporting format for the annual report. However, you may choose to use a different format. In either case, we request that you include the information listed below in your report. See appendices for examples of annual reports.

- We ask that you submit a cover letter describing the contents of your annual report.

- Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use (FDA Form 356h) (Ref. 5).
    1. Include U.S. license number of the manufacturer.
    2. Identify the time period covered in the report.

- Description of the current organizational systems involved in the manufacture of Whole Blood and blood components, to include any quality assurance activities.
    1. If organizational changes have occurred since the last report, submit a current organization chart with descriptive job titles.
    2. List the licensed products you are currently approved to distribute in interstate commerce.

- Full description of minor changes reported to approved applications, as described in section VI.
    1. List products affected by each change.
    2. List the address of the facility or facilities where the change was implemented. Include the registration number of the facility.
    3. Include the date the change became effective.
    4. Reference any approved CPs used to implement the change.
    5. Describe the SOP or process affected by the change.

VII. COMPARABILITY PROTOCOL UNDER 21 CFR 601.12(e)

A. Description of a Comparability Protocol (CP)

The CP described in 21 CFR 601.12(e) is a supplement that establishes the tests to be done and acceptable limits to be achieved to demonstrate the lack of adverse effect for specific manufacturing changes on the safety or effectiveness of the product. A CP is a highly specific, well-defined plan for the future implementation of a Chemistry, Manufacturing and Controls (CMC) change. The purpose of a CP is to allow for a more expedient distribution of product by permitting you to submit a protocol for a change, which if approved, may justify a reduced reporting category for the particular change at the time the change is implemented. A new CP, or a change to an existing one, requires approval prior to implementation because it may result in a decreased reporting category for the changes covered in the CP (e.g., PAS to CBE30). The reporting category will be established at the time that the CP is approved.

You may wish to receive our input on your implementation plans prior to commencing your activities. For example, you could submit your validation plan as a CP for our review in advance of implementing any change. This may allow you to make future changes more expeditiously.

B. Applicability of a Comparability Protocol

You should assess if the use of a CP is appropriate for the specified manufacturing change. Generally, the change should be a discrete, specific manufacturing change in a facility, equipment, or process. There should be sufficient manufacturing experience and acceptance criteria available to demonstrate that the change does not have an adverse effect on the safety or effectiveness of the product. A CP should only be considered if:

1. The product manufactured using the change will meet approved product standards.
2. The manufacturing process has been validated and all equipment qualified.
3. Appropriate validated assays are available to evaluate the effect of the change on the product.

We have experience with several types of traditional CMC protocols that would be appropriate for a CP. These include a change with a long planning or development cycle but a short implementation window or a change that will be repeated several times by the applicant in a similar, but not identical way. Examples of changes for which a CP might be useful are:

1. Acquisition of facilities operating under one manufacturer's license by another

licensee.

2. Single change in the manufacture of a product that will be implemented in multiple facilities under a single license, e.g., plateletpheresis.
3. Change to use a cleared apheresis device for the collection of products approved for this device, e.g., use of Fenwal Amicus to also collect Platelets, Pheresis; Platelets, Pheresis, Leukocytes Reduced; and Fresh Frozen Plasma, concurrently with plateletpheresis.

The use of a CP is not appropriate for all manufacturing changes. Certain changes may be too critical, complex, or of such a magnitude that a CP cannot be designed to adequately evaluate the effect of the change on the safety and effectiveness of the product. In such cases, you would need a PAS to implement the change. Also, changes already reported as CBE or in the annual report would have little benefit as a CP. In general, the use of a CP is not appropriate for:

1. Broad ranging plans, covering any conceivable change in the manufacturing process.
2. A change with the potential to adversely affect the product.
3. A change where pre-specified acceptance criteria are not available to determine the effect of the change on the product.
4. A change resulting in a newly characterized product that is not currently licensed.
5. The use of a new manufacturing facility for which we would normally conduct a pre-license inspection.
6. A change in a facility, equipment or process for which we would normally conduct a pre-approval inspection.

C. Content of a Comparability Protocol Submission

In addition to the information usually submitted in a prior approval supplement, you should include some or all of the following in a CP:

1. Description of the planned manufacturing change;
2. Implementation plan;
3. Specific tests and validation protocols (include the rationale for selecting the specific tests and protocols);
4. Criteria for acceptance of product prepared under changed conditions;
5. Description of actions taken if the acceptable results are not achieved;
6. Supportive data obtained from selected testing;
7. Training program;
8. Quality assurance program, including quality control testing plan;
9. Product submission sampling plan; and
10. Proposed change in reporting category.

D. Submission of a Comparability Protocol and Reporting of the Manufacturing Change(s) Implemented Using an Approved Comparability Protocol

You should submit the CP as a PAS and describe how you will implement a manufacturing change. You should submit the actual change implemented using the approved CP in the reporting category that we had specified in the approval letter (e.g., CBE30). In the second submission, you should describe the change, refer to the approved CP, and include all the data committed to be collected under the CP.

The CP may contain supportive data and a request to distribute product made with the specified manufacturing change or may only contain the implementation procedures described in VII.C. with a request to review and approve the CP before the supportive data are generated. If the CP is accompanied by supporting data and is approved, the product made using the change described in the CP can be distributed. If the CP is approved prior to the generation of data supporting the change, the supportive data should be submitted in the reduced reporting category we specified in the approval letter.

E. Failure to Meet the Criteria of an Approved Comparability Protocol

During the implementation of changes using an approved CP, you may discover instances with unpredicted or unwanted outcomes and you must deviate from the protocol to resolve the problems, deficiencies, or discrepancies. In such cases, you may elect not to make the change, request that the CP be withdrawn, and report the change as a PAS instead of the reporting category we specified when the CP was approved. You should contact us as soon as possible to discuss the proper application procedure.

F. Additional Considerations of a Comparability Protocol

Technical innovations may change the procedures and parameters specified in an approved CP and may render the CP obsolete. If you are using an approved CP, you should routinely review the procedures and specifications in the CP to assure that they remain current and consistent with the applicable application and current guidance. If modifications are required, you should withdraw the current CP and submit the modified CP as a PAS.

VIII. LABELING CHANGES UNDER 21 CFR 601.12(f)

Under 21 CFR 601.12(f), you must report changes to labeling in one of the following ways:

1) As a supplement requiring FDA approval prior to distribution of a product with the labeling change [21 CFR 601.12(f)(1)];
2) as a supplement requiring FDA approval but permitting distribution of a product bearing such change prior to FDA approval [21 CFR 601.12(f)(2)]; or
3) in an annual report [21 CFR 601.12(f)(3)].

We have listed below examples of changes to labeling (product labels, circular of information, package inserts) that we currently consider to be appropriate for submission in each of the categories.* This list is not intended to be all-inclusive. A completed Form FDA 2567 "Transmittal of Labels and Circulars Form" should accompany each submission.

***NOTE:** Report changes in the content of the label. Product labels must be consistent with requirements stated in 21 CFR 606.121 for Whole Blood and blood components and in 21 CFR 640.70 for Source Plasma and should be consistent with recommendations in published guidance. You do not need to report changes in format only.

A. Labeling changes requiring approval prior to product distribution [21 CFR 601.12(f)(1)]: Where applicable, circular of information must also be submitted as part of the labeling submission. (NOTE: A current circular of information does not have to be submitted if it is already in your file at FDA.)

1. Labels submitted as part of a pending application or Prior Approval Supplement.
2. Labeling which contains an additional claim. You may need to provide documentation to support these claims.
3. Labels representing a change in the volume of Whole Blood collected, e.g., 450 mL. to 500 mL., with an approved SOP stating donor must weigh at least 110 lbs.
4. If you are already approved to manufacture Source Plasma for injectable products and now want to include the manufacture of Source Plasma for non-injectable products, you should submit your non-injectable product label(s) in this category.
5. If you are already approved to manufacture Source Plasma for non-injectable products and now want to include the manufacture of Source Plasma for injectable products, you should submit your injectable product label(s) in this category.
6. Green base labels for units intended for autologous use only and labels printed using black ink for all text (exemptions to 21 CFR 606.121 approved as 21 CFR 640.120 variance).

7. Conversion from Codabar to ISBT128 labels.

B. Labeling changes requiring FDA approval but product may be distributed prior to FDA approval [21 CFR 601.12(f)(2)]:

1. Labels submitted as part of a Changes Being Effected (CBE30 or CBE) supplement.
2. Labels consistent with an FDA-approved uniform Codabar labeling guideline.
3. Print on-demand, black and white ABO/Rh labels.
4. Labels representing a change in FDA-approved additive/anticoagulant solutions used in blood product collection.

C. Labeling changes requiring submission in an annual report [21 CFR 601.12(f)(3)]:

1. Labels for Source Plasma collected from normal donors with pre-existing disease-associated, red blood cell and/or HLA antibodies.
2. Labels representing a change in "doing business as" name that does not affect the legal entity name on the license. Your legal entity name should appear on the label.

IX. FAILURE TO COMPLY UNDER 21 CFR 601.12(g)

In addition to other remedies available in the law and regulations, if you repeatedly fail to comply with 21 CFR 601.12, we may require that you submit a supplement for any proposed change and obtain our approval of the supplement prior to distribution of the product made using the change.

X. REFERENCES

1. Federal Register, 7/24/97 (62 FR 39890), Final Rule: Changes to an Approved Application. (http://www.fda.gov/cber/rules/chng072497.htm)

2. Federal Register, 7/24/97 (62 FR 39904), Guidance for Industry: Changes to an Approved Application: Biological Products, July 1997. (http://www.fda.gov/cber/gdlns/chbiol.txt) (or substitute pdf for txt in the URL)

3. Federal Register, 10/29/97 (62 FR 56193), Workshop on the Biologics License Application (BLA) for Blood Products and Reporting Changes to an Approved Application, December 2, 1997. Sponsored by FDA, CBER.

4. Federal Register, 10/20/99 (64 FR 56441), Final Rule: Biological Products Regulated Under Section 351 of the Public Health Service Act; Implementation of Biological License; Elimination of Establishment License and Product License. (http://www.fda.gov/cber/rules/elapla.txt) (or substitute pdf for txt in the URL)

5. Federal Register, 5/10/99 (64 FR 25049), Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use," May 1999. (http://www.fda.gov/cber/gdlns/cmcblood.txt) (or substitute pdf for txt in the URL)

6. Revised Form FDA 356h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use. (http://www.fda.gov/opacom/morechoices/fdaforms/cber.html)

7. Workshop for Licensing Blood Establishments, January 30 & 31, 1995. Sponsored by FDA, CBER.

8. Federal Register, 5/14/96 (61 FR 24227), Final Rule: Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products. (http://www.fda.gov/cber/rules/ela051496.pdf)

9. Federal Register, 10/15/97 (62 FR 53536), Final Rule: Revision of the Requirements for a Responsible Head for Biological Establishments. (http://www.fda.gov/cber/genadmin/resphead.htm)

10. Federal Register, 11/25/92 (57 FR 55544), Notice: FDA's Policy Statement Concerning Cooperative Manufacturing Arrangements for Licensed Biologics.

11. Draft Reviewer's Guide: "Disease Associated Antibody Collection Program," October 1, 1995. (by fax at 888-CBER-FAX)

12. Memorandum to All Licensed Manufacturers of Source Plasma: "Physician Substitutes," August 15, 1988. (http://www.fda.gov/cber/bldmem/081588.txt) (or substitute pdf for txt in the URL)

APPENDIX A: Sample of a Blood Bank Annual Report

Annual Report for Community or Hospital Blood Bank
123 Sunshine Drive
Any town, USA xxxxx
U.S. License Number xxxx
Registration # xxxxxxx

Reporting period: January 1, 1998 to December 31, 1998

XYZ Blood Establishment is currently licensed to manufacture:

Whole Blood; Red Blood Cells; Platelets; Platelets, Pheresis; Fresh Frozen Plasma; Red Blood Cells, Irradiated; Platelets, Leukocytes Reduced; Source Plasma

See attached organizational chart, including a list of all facilities and contractors.

Equipment changes:

March 1, 1998

Removal of all Fenwal CS3000 and using Cobe Spectra exclusively for Platelets, Pheresis.

August 1, 1998

Implement use of computerized donor information system. LAN at all transfusion centers, Mainframe at Reg. No. xxxxxxx

Facility changes:

June 13, 1998

Closed Whole Blood Donor Center at 321 Sunshine Dr., Anytown, USA (Reg. No. xxxxxxx).

Procedure changes:

September 10,1998

Implemented Anti-HTLV-II testing in accordance with FDA guidance document (8/97). At the same time changed from Abbott HTLV-I EIA assay to Abbott HTLV-I/II EIA assay.

Contractual changes:

None