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

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Guidance for Industry

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For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
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Guidance for Industry

This guidance represents the Food and Drug Administration's (FDA's or Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, FDA, are providing you, manufacturers of licensed Whole Blood and blood components intended for transfusion or for further manufacture, including Source Plasma, with recommendations intended to assist you in determining which reporting mechanism is appropriate for submission of changes to an approved Biologics License Application (BLA) in accordance with the requirements under Title 21 of the Code of Federal Regulations (CFR) 601.12 (21 CFR 601.12), including recommendations in connection with the applicability and content of comparability protocols under 21 CFR 601.12(e) and labeling changes under 21 CFR 601.12(f).

This guidance finalizes the draft guidance of the same title dated June 2013 (78 FR 32668, May 31, 2013) and supersedes the guidance entitled, "Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture" dated July 2001 (66 FR 41247, August 7, 2001) (Ref. 1).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Frequently, a manufacturer of a licensed product determines that it is appropriate to make a change in its product, production process, quality controls, equipment, facilities, responsible personnel, or labeling. Section 601.12 (21 CFR 601.12) states the requirements for you to report such changes for your licensed biological products to FDA.

Under 21 CFR 601.12, you must report each change in the product, production process, quality controls, equipment, facilities, responsible personnel or labeling established in the approved license application to FDA in one of the following categories of submissions:

- a supplement which must be approved before distribution of the product made using the change;
- a supplement submitted at least 30 days before distribution of the product made using the change; or
- as a change described in an Annual Report (AR).

The submission category depends on the potential for the change to have an adverse effect on the "identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product" (Ref. 2) (referred to in this document as "the safety or effectiveness of the product"). Before distributing a licensed product made using a change from the approved BLA, you are required to assess the effects of the change and demonstrate, through appropriate validation and/or other clinical and/or non-clinical laboratory studies, the lack of an adverse effect of the change on the safety or effectiveness of the product (21 CFR 601.12(a)(2)).

The three reporting categories into which a change to an approved application may be placed are defined in 21 CFR 601.12 and are as follows:

- **Major Change.** A change that has a substantial potential to have an adverse effect on the safety or effectiveness of the product. Major changes require the submission of a Prior Approval Supplement (PAS) to FDA, which FDA must approve before you distribute the product made using the change (21 CFR 601.12(b)).

- **Moderate Change.** A change that has a moderate potential to have an adverse effect on the safety or effectiveness of the product. Moderate changes require the submission of a Changes Being Effected in 30 Days Supplement (CBE30) to FDA at least 30 days before you distribute the product made using the change (21 CFR 601.12(c)). In certain circumstances, FDA may determine that the product made using the change may be distributed immediately upon receipt of the Changes Being Effected Supplement (CBE) by FDA (21 CFR 601.12(c)(5)).

- **Minor Change.** A change that has a minimal potential to have an adverse effect on the safety or effectiveness of the product. Minor changes must be described by the applicant in an AR (21 CFR 601.12(d)).

If you make a change to an approved BLA, 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 (FD&C Act) (21 U.S.C. 351(a)(2)(B)) and the regulations in 21 CFR Parts 210, 211 and Parts 600 through 680. For example, you must comply with the relevant recordkeeping requirements (21 CFR 600.12) and ensure that the relevant records are readily available for examination by authorized FDA personnel during an inspection (21 CFR 600.22). The recommendations contained in this guidance reflect current FDA and industry experience with reporting changes to an approved BLA, including reporting the implementation of new technologies. Based on our experiences, we have revised recommendations that were in the July 2001 Guidance for reporting categories for certain changes to an approved application. In addition, this guidance has been updated to include recommendations for reportable changes that were not included in the July 2001 Guidance.

If you have questions concerning which reporting category is appropriate, you may contact FDA prior to submitting a supplement.

III. DEFINITIONS

The following terms are defined for the purpose of this document:

Acquisition: The purchase of a facility previously operated under one United States (U.S.) license number by a manufacturer holding a different U.S. license number or by a new applicant. This also includes combining facilities operating under different licenses owned by the same corporation so that there is only one surviving license number. **Note:** Once the acquisition is complete, the acquired facility will no longer be associated with 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 products at the acquired facility. If a new applicant has acquired a facility, we will grant a new license (Ref. 3). See Appendix B of this guidance.

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) (42 U.S.C. 262). **Note:** The applicant assumes responsibility for compliance with the applicable product and establishment standards and for quality assurance (QA) oversight of all manufacturing steps (Ref. 4).

AR (Annual Report): A report describing changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on the safety or effectiveness of the product (21 CFR 601.12(d)). Labeling changes requiring submission in an AR are described in 21 CFR 601.12(f)(3).

Authorized Official: A person designated by the applicant to communicate with FDA on behalf of the applicant. **Note:** An authorized official can initiate applications or supplements to a license application, discuss submissions and product correspondence with FDA representatives,

provide additional information in support of the submissions, and withdraw applications or supplements (Ref. 5). The applicant should immediately notify FDA in writing if there is a change in the authorized official.

BLA (Biologics License Application): An application for a biologics license to manufacture and distribute in interstate commerce a product subject to licensure under section 351 of the PHS Act, including supportive documentation (Ref. 6).

Blood Product: A drug which consists of human whole blood, plasma or serum or any product derived from human whole blood, plasma or serum (21 CFR 607.3(b)).

Circular of Information: Required labeling that must be available for distribution with Whole Blood or blood components intended for transfusion. The circular of information must provide adequate directions for the use of blood and blood components intended for transfusion, including the following information: a description of the blood product; information on the tests performed for communicable disease agents; indications for use; contraindications; side effects and hazards; dosage and administration recommendations (21 CFR 606.122) (Ref. 7).

CBE (Changes Being Effected Supplement): A supplement submission for a change that has a moderate potential to have an adverse effect on the safety or effectiveness of the product which may be implemented any time after FDA receives the submission describing the change.

CBE30 (Changes Being Effected in 30 Days Supplement): A supplement submission for certain changes that have a moderate potential to have an adverse effect on the safety or effectiveness of the product which FDA receives at least 30 days before the distribution of the product made using the change.

Computer-Assisted Interactive Interview: The administration of questions to potential donors using a computer system without direct oral questioning by donor screening personnel. The software program may make donor eligibility decisions based on the potential donor's responses. There are non-web-based computer-assisted interactive interview software programs, which can be accessed at a firm's fixed locations or mobiles and web-based computer-assisted interactive interview software programs, which permit potential donors to have remote access to the donor history questionnaire via the Internet (Ref. 8). **Note:** This definition does not apply to computer programs used to display questions to a blood establishment's donor screening personnel who administer the questions to the potential donor by direct oral questioning and enter the donor's responses into the computer.

Contractor: Any person or entity, other than the applicant, that performs part or all of the manufacturing of a licensed product as a service to the applicant under a contract. **Note:** The applicant is responsible for determining that a contractor is in compliance with applicable FDA requirements (Ref. 9). All contractors performing a manufacturing step for a licensed product must be registered with FDA, unless they are exempt from registration (21 CFR Part 607).

Contractual Agreement: Written legal agreement between a manufacturer and a contractor that describes the manufacturing steps performed by the contractor. **Note:** Although the firm does not need to include the specific legal contract in the submission, the submission should include a description of the services performed by the contractor for each manufacturing step, for example, the performance by an outside testing laboratory of routine donor/product testing or confirmatory testing, the irradiation of products, the supply of red blood cells for immunization, or the provision of storage services. The agreement should also be available for review during inspections.

Core Personnel: Establishment/facility management, medical personnel and staff responsible for quality oversight.

Comparability Protocol (CP): A PAS describing the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effects for specified types of manufacturing changes on the safety or effectiveness of the product, which must be approved by FDA before distribution of the product (21 CFR 601.12(e)).

Disease-Associated IgG Antibody Donor: A donor who meets all the required or recommended normal Source Plasma donor eligibility criteria and whose plasma contains pre-existing IgG antibodies as a result of previous exposure to certain diseases or cellular antigens (Ref. 10).

Disease-State/High-Risk Donor: A donor whose plasma contains or lacks a specific property (for example, a protein, antibody, inherited trait) as a result of the donor's disease. **Note:** This donor may not meet all the required or recommended Source Plasma donor eligibility criteria but nonetheless may be an acceptable donor under certain circumstances.

eSubmitter: An electronic submissions program that is currently available for voluntary use by sponsors, manufacturers, and importers to submit a variety of submission types for FDA-regulated products. eSubmitter is an acceptable mechanism for the submission of BLAs, BLA supplements, annual reports and amendments to pending eSubmitter regulatory submissions by licensed blood establishments that collect Whole Blood and blood components, including Source Plasma (Ref. 11).

Establishment/Facility: A place of business under one management at one general physical location. The term includes, among others, human blood and plasma donor centers, blood banks, transfusion services, other blood product manufacturers and independent laboratories that engage in quality control and testing for registered blood product establishments. **Note**: The facility in which a biological product is manufactured, processed, packed or held must meet standards designed to assure that the biological product continues to be safe, pure and potent (PHS Act) (42 U.S.C. 262(a)(2)(C)(i)(II)). The term "establishment" has the same meaning as "facility" and includes all locations (21 CFR 600.3(w)) (Ref. 12).

Types of Facilities:

- **Collection Facility:** A facility that collects Whole Blood and/or apheresis products, and/or performs plasmapheresis collected by manual or automated methods, but does not perform FDA required or recommended blood and plasma donor testing. Collection facilities may also label, store, and distribute blood products.

- **Community Blood Bank:** A commercial or non-profit blood collection/processing facility, not located in a hospital, that may perform manual and/or automated blood collection, prepare components from Whole Blood, perform FDA required or recommended blood and plasma donor testing, perform compatibility testing and that 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, pre-storage pooled Platelets and pre-storage pooled Cryoprecipitated AHF.

- **Component Preparation Facility:** An intermediate processing facility that prepares components from Whole Blood or further processes apheresis components 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 label, store, and distribute blood products and/or may prepare irradiated, frozen, deglycerolized and/or leukoreduced products, pre-storage pooled Platelets and pre-storage pooled Cryoprecipitated AHF.

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

- **Plasmapheresis Center:** A facility that collects Source Plasma by manual and/or automated methods. Plasmapheresis centers may also perform FDA required or recommended plasma donor testing.

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

- **Distribution Center:** A facility that stores Whole Blood or blood components under specific controlled conditions prior to shipment to the final user, including suppliers of source material for further manufacture, such as recovered plasma and Source Plasma or Whole Blood, Red Blood Cells, or Platelets for diagnostic use; for example, Source Plasma warehouses that intend to redistribute the product to fractionators or recovered plasma holding facilities or brokers that intend to redistribute the product to diagnostic

device 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.

Inspection: A careful, critical, official evaluation conducted by FDA personnel of operations at an establishment to assess whether the establishment is in compliance with applicable laws and regulations and the standards established in the BLA.

Types of Inspection:

- **Pre-License Inspection:** An announced inspection conducted by a team of the Center for Biologics Evaluation and Research (CBER) inspectors and/or Office of Regulatory Affairs (ORA) investigators. This comprehensive inspection is conducted as part of the review of an application for a U.S. license for a new product by an establishment that has not previously manufactured a licensed product.

- **Pre-Approval Inspection:** An announced or unannounced inspection conducted by inspectors from CBER and/or investigators from ORA, FDA. This inspection is conducted as part of the review of a supplement to an approved BLA. **Note:** Examples of supplements that would require a pre-approval inspection include submissions for an additional new facility operating under an existing U.S. license, the manufacture of irradiated blood products, or implementation of a red blood cell immunization program under a Source Plasma 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 blood establishments are in compliance with applicable laws and regulations and with commitments made in the approved license application. 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 inspect selected operations of an establishment. Examples of directed inspections include a follow-up to a fatality report or consumer complaint.

Manufacture: The collection, preparation, processing or compatibility testing by chemical, physical, biological or other procedures of any blood product which meets the definition of a drug, as defined in section 201(g) of the FD&C Act, including manipulation, sampling, testing or control procedures applied to the final product or to any part of the process. The term includes packaging, labeling, repackaging or otherwise changing the container, wrapper, or labeling of any blood product package in furtherance of the distribution of the blood product from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer (21 CFR 607.3(d)). The term means all steps in propagation or manufacture and preparation of products and includes, but is not limited to, filling, testing, labeling, packaging, and storage by the manufacturer (21 CFR 600.3(u)).

Manufacturer: Any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act. The term also includes any legal person or entity who 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. The term may also be used to describe the instructions in equipment operator's manuals and product labels.

Merger: A union of two or more licensed manufacturers to form a new legal entity (See SOPP 8403: Issuance and Reissuance of Licenses for Biological Products) (Ref. 13).

Prior Approval Supplement (PAS): A supplement submission for a major change that has a substantial potential to have an adverse effect on the safety or effectiveness of the product and for which distribution of the product made using the change cannot occur before FDA approval is obtained (21 CFR 601.12(b)).

Product Correspondence: Any communication from a manufacturer to FDA, excluding ARs, that is not related to a pending supplement or application. Examples of product correspondence include changes in corporate mailing addresses or a change in or addition of, an authorized official. **Note:** Product correspondence is not a reporting category under 21 CFR 601.12.

Self-Administered Questionnaire: Questionnaire in which the donor reads or listens to the medical/health history questions and/or high-risk questions and documents his/her answers. A self-administered questionnaire process allows a donor to answer the pre-donation screening questions without direct oral questioning by collection personnel (Ref. 8).

Supplement: Request submitted to the Director, CBER, to approve a change in an approved license application (21 CFR 600.3(gg)).

IV. RECOMMENDATIONS

In this guidance document, we provide examples of changes to be submitted in each reporting category described in 21 CFR 601.12. These examples are not intended to be all-inclusive and the recommended reporting categories may change as new products and technologies become available.

When you implement recommendations contained in a specific guidance document, you should report the changes to FDA in accordance with the instructions in that specific guidance document.

A. 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) – Reporting Category (PAS)

Under 21 CFR 601.12(b), if you make any change to your product, production process, quality controls, equipment, facilities or responsible personnel 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 approval from FDA prior to distribution of the product made using the change. You must submit product manufacturing/procedural changes, equipment changes, contractor changes and facility changes in a PAS, as required under 21 CFR 601.12(b), unless this guidance specifies that the change may be reported in another category. Labeling changes requiring submission in a PAS are described in 21 CFR 601.12(f)(1).

Under 21 CFR 601.12(b)(3), for a change under this category, you must submit a supplement to your approved BLA that includes the following:

- a detailed description of the proposed change;
- the product(s) 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 such studies;
- relevant validation protocols and data; and
- a reference list of relevant Standard Operating Procedures (SOPs). In some cases, we may recommend submission of a complete set of SOPs describing all manufacturing impacted by the proposed change. Please refer to the FDA guidance to industry entitled, "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'" dated May 1999 (May 1999 Guidance) (Ref. 14).

In addition, if the change involves a change in labeling, you must follow the requirements in 21 CFR 601.12(f), discussed in section VI of this guidance.

Refer to the following appendices for examples of applicable changes:

- Appendix B: Reporting Facility Changes
- Appendix C: Reporting Changes in Facility Relocations
- Appendix D: Reporting Changes Associated with Blood Establishment Computer Software (BECS)
- Appendix E: Reporting Changes in Apheresis Operations and Automated Blood Separator Devices

- Appendix F: Reporting Changes in Source Plasma/Immunization Programs for Source Plasma Donors
- Appendix G: Reporting Changes in Manufacture of Leukocytes Reduced Blood Components
- Appendix H: Reporting Contract Changes
- Appendix I: Reporting Changes in Donor History Questionnaires
- Appendix J: Reporting Changes in Standard Operating Procedures (SOPS)
- Appendix K: Reporting Changes in Equipment
- Appendix L: Reporting Product Manufacturing/Procedural Changes

B. 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) – Reporting Category (CBE30)

Under 21 CFR 601.12(c), if you make any change to your product, production process, quality controls, equipment, facilities or responsible personnel that has a moderate potential to have an adverse effect on the safety or effectiveness of the product, you must submit a supplement to FDA at least 30 days prior to distribution of the product made using the change. The information contained in the supplement is the same as for a PAS (See 21 CFR 601.12(b)(3)).

You must specify that the changes are being reported in this category by labeling the submission: "Supplement - Changes Being Effected in 30 Days" (21 CFR 601.12(c)). 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.

Note: 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 have been reported in the proper category.

We will not notify you when we receive your CBE30 supplement; instead, we recommend that you have a mechanism to track the date we received the supplement submission; for example, a courier 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 problem(s) 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.

Refer to the following appendices for examples of applicable changes:

- Appendix B: Reporting Facility Changes
- Appendix C: Reporting Changes in Facility Relocations
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- Appendix G: Reporting Changes in Manufacture of Leukocytes Reduced Blood Components
- Appendix H: Reporting Contract Changes
- Appendix I: Reporting Changes in Donor History Questionnaires
- Appendix J: Reporting Changes in Standard Operating Procedures (SOPS)
- Appendix K: Reporting Changes in Equipment
- Appendix L: Reporting Product Manufacturing/Procedural Changes

C. Changes under 21 CFR 601.12(c)(5) - Changes Requiring Supplement Submission Before Distribution of the Product Made Using the Change But Such Product May Be Distributed Immediately Upon FDA's Receipt of the Supplement – Reporting Category (CBE)

As described in 21 CFR 601.12(c)(5), in certain circumstances, we may determine that, based on our experience with a particular type of change, 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, as mentioned in section IV.B. of this guidance. Labeling changes requiring submission in a CBE are described in 21 CFR 601.12(f)(2).

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.

Note: 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 change is 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 problem(s) 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.

Refer to the following appendices for examples of applicable changes:

- Appendix B: Reporting Facility Changes
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- Appendix L: Reporting Product Manufacturing/Procedural Changes

D. Changes under 21 CFR 601.12(d) - Changes to be Described in an Annual Report (Minor Changes) – Reporting Category (AR)

Under 21 CFR 601.12(d), you must document changes to the product, production process, quality controls, equipment, facilities or responsible personnel that have minimal potential to have an adverse effect on the safety or effectiveness of the product in an AR 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(s) in your AR. Labeling changes requiring submission in an AR are described in 21 CFR 601.12(f)(3).

Your first anniversary date is based on your first product approval. You may request an alternative date for the purpose of combining ARs for multiple approved applications into a single AR submission; such a request must be in writing (21 CFR 601.12(d)(1)). We will notify you if your alternative date is acceptable. If so, the alternate date will become your new anniversary date and the combined report must be submitted within 60 days of this date.

You should submit one original AR and two copies to FDA for review. If there are no minor changes to report, you need not submit an AR.

We will review the AR to determine if the changes were reported in the proper category. If the AR 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 AR. 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.

Refer to the following appendices for examples of applicable changes:

- Appendix B: Reporting Facility Changes
- Appendix C: Reporting Changes in Facility Relocations
- Appendix D: Reporting Changes Associated with Blood Establishment Computer Software (BECS)
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- Appendix K: Reporting Changes in Equipment
- Appendix L: Reporting Product Manufacturing/Procedural Changes

1. Information that should <u>not</u> be included in the AR:

    a. Major or moderate changes that have received FDA approval as supplements during the reporting period, unless they are included in the organizational changes.

    b. Major or moderate changes submitted as supplements and currently under our review.

c. Shipment of inadvertently collected Source Plasma that is repeatedly reactive or positive for an infectious disease marker and is to be used in the manufacture of vaccines and in vitro diagnostic biological products. You must report these shipments in the manner stated in 21 CFR 610.40(h)(2).

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. If the development of unexpected antibodies is due to an error in immunization practices, you must report this under 21 CFR 606.171.

e. Biological product deviation reports, and fatalities as a result of complications of blood collection or transfusion. You must report these events as provided under the reporting requirements (21 CFR 606.170 and 606.171).

f. 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 by FDA during inspections, unless FDA has requested it for a specific submission, for example, a CP.

g. Information usually contained in a product correspondence (PC), for example, a change in corporate mailing address of the legal entity, a change in, or addition of, an authorized official, or a request to change an AR date.

Note: The PC describes changes that may or may not require a review and/or approval. A PC does not normally require a response from FDA. The examples listed are not intended to be all-inclusive.

2. Reporting format for the AR

We recommend that you use the following reporting format or eSubmitter for the AR. However, you may choose to use a different format. In either case, you should include the information listed below in your report.

a. A cover letter summarizing the contents of your AR (for hard copy submissions only).

b. A completed Form FDA 356h, “Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use” (Ref. 6). The form should include, reflect or identify:

i. Your U.S. license number; and
ii. The time period covered in the report.

c. A description of changes to the organizational systems involved in the manufacture of Whole Blood and blood components, including any quality assurance activities. This description may include the following information:

i. If organizational changes have occurred since the last report, a current organization chart (optional) with descriptive job titles; and
ii. A list of the licensed products (optional) you are currently approved to distribute in interstate commerce.

d. A full description of minor changes reported to approved applications. This description should include:

i. The products affected by each change;
ii. The facility or facilities where the change was implemented; including their registration numbers;
iii. The date the change became effective;
iv. The Submission Tracking Number(s) (STNs) for any approved CPs used to implement the change; and
v. A description of the SOP or process affected by the change.

V. COMPARABILITY PROTOCOL (CP) UNDER 21 CFR 601.12(e)

A. Description of a Comparability Protocol

The CP described in 21 CFR 601.12(e) and submitted in a PAS, establishes the specific tests and validation studies to be done and acceptable limits to be achieved to demonstrate the lack of adverse effect for specific types of manufacturing changes on the safety or effectiveness of a product. 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 (as approved in the CP). 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 (for example, PAS to CBE30). The reporting category for the changes themselves will be established at the time that the CP is approved.

B. Applicability of a Comparability Protocol

1. You should assess whether the use of a CP is appropriate for the specific type of 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:

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

2. We have experience with several types of traditional Chemistry, Manufacturing and Controls (CMC) protocols that would be appropriate for a CP. The CMC protocols 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:

    a. Acquisition of facilities operating under one manufacturer's license by another licensee (See Appendix B of this guidance);
    b. Single change in the manufacture of a product that will be implemented in multiple facilities under a single license, for example, plateletpheresis; and
    c. A change that has a long planning stage but a quick implementation turn-around time, for example, the relocation of a testing laboratory.

3. 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 or effectiveness of the product. In such cases, you would need to submit a PAS under 21 CFR 601.12(b) to implement the change. Also, changes already reported as CBE or in the AR would have little benefit as a CP. In general, the use of a CP is <u>not</u> appropriate for:

    a. Broad ranging plans, covering any conceivable change in the manufacturing process;
    b. A change with the potential to adversely affect the product;
    c. A change where pre-specified acceptance criteria are not available to determine the effect of the change on the product;

d. A change resulting in a newly characterized product that is not currently licensed;
e. The use of a new manufacturing facility for which we would normally conduct a pre-license inspection; and
f. 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 PAS, 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 (include data obtained during validation);
7. Description of training plan for the manufacturing change;
8. Summary of quality assurance plan for the manufacturing change, including quality control testing plan;
9. Product statistical sampling plan; and
10. Proposed change in reporting category.

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 specified in the approval letter (for example, CBE30). In submitting the change, you should describe the change, refer to the STN of 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 testing and validation procedures described in section V.C. of this guidance, 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.

D. 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 that require you to deviate from the protocol to resolve the problems, deficiencies, or discrepancies. In such cases, you may elect not to

make the change and request that the CP be withdrawn, or 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 submission procedure.

E. 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 regulations and current guidance. If modifications are required, you should contact us as soon as possible to discuss the proper application procedure. In some cases, you may need to withdraw the current CP and submit the modified CP as a PAS.

VI. 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 PAS requiring FDA approval prior to distribution of a product with the labeling change (21 CFR 601.12(f)(1)).

2. As a Labeling Supplement – Changes Being Effected requiring FDA approval but permitting distribution of a product bearing such change before FDA approves the supplement (21 CFR 601.12(f)(2)).

3. As a labeling change requiring submission in an AR (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 reporting categories. This list is not intended to be all-inclusive.

Note: Report changes in the content of the label. Product labels must be consistent with the regulations for Whole Blood and blood components including Source Plasma (21 CFR 606.121) and should be consistent with applicable recommendations in FDA guidance. You do not need to report changes in format only.

A. Labeling Changes Requiring FDA Approval Prior to Product Distribution (21 CFR 601.12(f)(1)) – Reporting Category (PAS)

1. Labels containing an additional claim with documentation to support these claims.

2. Labels representing a change in the volume of Whole Blood collected, for example, 450 mL to 500 mL. If you do not have an approved SOP that states donors must weigh at least 110 lbs, an accompanying SOP should be submitted for review.

3. Labels for products not currently licensed by FDA, when the establishment manufactures other licensed products. This may or may not also require concurrent submission and approval of new or revised standard operating procedures as described elsewhere in this guidance.

   For example:

   a. Labels for Source Plasma intended for further manufacture into noninjectable products, if the applicant is already approved to manufacture Source Plasma intended for further manufacture into injectable products.

   b. Labels for Plasma, Cryoprecipitate Reduced, if the applicant is already approved to manufacture Cryoprecipitated AHF and Fresh Frozen Plasma (FFP).

   c. Labels for Plasma Frozen within 24 Hours after Phlebotomy, if the applicant is already approved to manufacture FFP.

   d. Labels for the inadvertent manual collection of low volume Whole Blood or Red Blood Cells, if the applicant is already approved for the manufacture of Whole Blood and Red Blood Cells.

   e. Labels for blood and blood components intended for autologous use and obtained from a donor who is reactive for evidence of infection due to communicable disease agents.

4. The implementation of a new format for machine-readable labels, for example, conversion from “ABC Codabar” to the International Society of Blood Transfusion (ISBT) 128 labels.

5. Modification of an FDA-accepted Circular of Information where the modification impacts licensed blood components. A copy of the Circular of Information must be submitted for review (21 CFR 601.12(f)(1)).

B. Labeling Changes Requiring FDA Approval but Product May Be Distributed Prior to FDA Approval (21 CFR 601.12(f)(2)) – Reporting Category (Special Labeling Supplement – Changes Being Effected)

1. Print on-demand, black and white ABO/Rh labels.

2. Change in FDA-approved additive/anticoagulant solutions used in blood product collection.

3. Change in a blood establishment's "doing business as" name that does not affect the legal entity name associated with U.S. license number. **Note:** Your legal entity name must appear on the label (21 CFR 606.121(c)(2)).

4. Labels reflecting a legal name change or a change in a blood establishment's street address.

5. Labels showing the new legal name and U.S. license number when a non-license holder acquires all facilities from a license holder.

6. Labels for Source Plasma collected from normal donors with pre-existing disease-associated IgG antibodies, red blood cell and/or HLA antibodies (Ref. 10).

C. Labeling Changes Requiring Submission in an Annual Report (21 CFR 601.12(f)(3))

FDA-accepted Circular of Information without modification of the content.

VII. SUBMISSION OF CHANGES TO FDA

You should prominently label each submission with the reporting category under which you are reporting your change, for example, "Prior Approval Supplement," "Supplement - Changes Being Effected in 30 Days," "Supplement - Changes Being Effected," "Special Labeling 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 if the supplement is being submitted by hard copy or the supplement may be submitted by eSubmitter. For guidance in preparing a supplement, please refer to "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'" dated May 1999 (Ref. 14); and "Guidance for Industry: Availability of FDA's e Submitter Program for Regulatory Submissions from Licensed Blood Establishments" dated August 2011 (Ref. 11).

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. The May 1999 guidance describes the specific items that are to be included in a submission (Ref. 14).

You should report changes to your approved establishment, product, or biologics license applications to:

U.S. Food and Drug Administration
Center for Biologicals Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
WO71, G112
Silver Spring, MD 20992-0002

If you need further guidance, you should call the Division of Blood Components and Devices at (240) 402-8360.

VIII. 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 (21 CFR 601.12(g)).

IX. REFERENCES

1. Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture, July 2001.
2. Final Rule: "Changes to an Approved Application" (62 FR 39890, July 24, 1997). http://www.gpo.gov/fdsys/pkg/FR-1997-07-24/pdf/97-19427.pdf
3. Workshop: "FDA Regulation and Licensure of Whole Blood and Blood Components, Including Source Plasma," September 15 and 16, 2009. Sponsored by FDA, CBER. http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ ucm169497.htm
4. Final Rule: "Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products" (61 FR 24227, May 14, 1996). http://www.gpo.gov/fdsys/pkg/FR-1996-05-14/pdf/96-12144.pdf
5. Final Rule: "Revision of the Requirements for a Responsible Head for Biological Establishments" (62 FR 53536, October 15, 1997). http://www.gpo.gov/fdsys/pkg/FR-1997-10-15/pdf/97-27298.pdf
6. Form FDA 356h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use, November 2012. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM082348.pdf
7. Guidance for Industry: An Acceptable Circular of Information for the Use of Human Blood and Blood Components, Updated April 2014. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm364565.htm
8. Guidance for Industry: Streamlining the Donor Interview Process: Recommendations for Self-Administered Questionnaires, July 2003. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm075086.htm
9. Guidance for Industry: Cooperative Manufacturing Arrangements for Licensed Biologics, November 2008. http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm069908.pdf
10. Guidance for Industry: Implementing a Collection Program for Source Plasma Containing Disease-Associated and Other Immunoglobulin G (IgG) Antibodies, August 2006. http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm079673.pdf
11. Guidance for Industry: Availability of FDA's eSubmitter Program for Regulatory Submissions from Licensed Blood Establishments, August 2011. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm266499.htm

12. Final Rule: "Biological Products Regulated Under Section 351 of the Public Health Service Act; Implementation of Biologics License; Elimination of Establishment License and Product License" (64 FR 56441, October 20, 1999). http://www.fda.gov/OHRMS/DOCKETS/98fr/102099a.pdf

13. SOPP 8403: Issuance and Reissuance of Licenses for Biological Products, September 21, 2010. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073468.htm

14. 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/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm077087.htm

15. Guidance for Industry: Implementation of an Acceptable Abbreviated Donor History Questionnaire and Accompanying Materials for Use in Screening Frequent Donors of Blood and Blood Components, May 2013. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm351107.htm

16. Guidance for Industry: Implementation of Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for Use in Screening Donors of Blood and Blood Components, October 2006. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm073445.htm

17. Guidance for Industry: Recommendations for Blood Establishment: Training of Back-Up Personnel, Assessment of Blood Donor Suitability and Reporting Certain Changes to an Approved Application, November 2010. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm235785.htm

18. Guidance for Industry: Recommendations for Management of Donors at Increased Risk for Human Immunodeficiency Virus Type 1 (HIV-1) Group O Infection, August 2009. http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM180844.pdf

APPENDIX A: TYPES OF ESTABLISHMENTS/FACILITIES AND MANUFACTURING STEPS PERFORMED

Manufacturing Steps Performed	Collection Facility	Community Blood Bank	Component Preparation Facility	Hospital Blood Bank	Plasmapheresis Center	Product Testing Laboratory	Distribution Center
Manual Whole Blood collection	X	X		X	X		
Whole Blood component preparation		X	X	X	X		
Automated plateletpheresis	X	X		X			
Automated RBC apheresis	X	X		X			
Automated plasmapheresis	X	X		X	X		
Manual plasmapheresis	X	X		X	X		
Product testing		X		X	X	X	
Labeling	X	X	X	X	X		
Storage	X	X	X	X	X		X
Distribution	X	X	X	X	X		X
Irradiation		X	X	X			
Freeze/deglycerolize		X	X	X	X		
Leukocyte reduction – does not include bedside filtration		X	X	X			
Compatibility testing		X		X			
Pre-storage pooling of Platelets and Cryoprecipitated AHF		X	X	X			

APPENDIX B: REPORTING FACILITY CHANGES

FACILITY OPERATION	CHANGE PERFORMED	BLA Note: BLA is not a reporting category under 21 CFR 601.12	Reporting Category PAS	CBE30	CBE	AR	PC Note: Product correspondence is not a reporting category under 21 CFR 601.12
Facility Closures	Partial Closure: Manufacturer permanently closes some, but not all, of its licensed manufacturing facilities.						X
	Closure of fixed donor sites that perform only manual Whole Blood collections.					X	
	Temporary closure of a facility.					X	
	Complete Closure: U.S. license holder permanently closes all of its manufacturing facilities and voluntarily requests revocation of the relevant product licenses.						X
Facility Openings	U.S. license holder expands its operations to include the opening of a new collection facility for Platelets, Pheresis Leukocytes Reduced under an approved CP.			X			
	U.S. license holder opens a fixed donor site that performs only manual Whole Blood collections.					X	
	U.S. license holder reopens a facility after temporary closure provided there are no changes in SOP, major equipment, procedures or core center personnel.					X	
	U.S. license holder expands its operations to include the opening of a Source Plasma collection center.		X				

APPENDIX B: REPORTING FACILITY CHANGES

FACILITY OPERATION	CHANGE PERFORMED	BLA Note: BLA is not a reporting category under 21 CFR 601.12	Reporting Category PAS	CBE30	CBE	AR	PC Note: Product correspondence is not a reporting category under 21 CFR 601.12
	U.S. license holder expands operations by adding a facility where licensed products are manufactured. This includes the addition of a contractor to perform the manufacturing step(s). Examples of such facility changes include adding: Facilities where Red Blood Cells, Fresh Frozen Plasma, Platelets, and Pheresis products are collected using automated blood cell separators, and Source Leukocytes are collected using either manual or automated collection methods, or where routine FDA required or recommended blood and plasma testing is performed.		X				
Self-Contained Collection Vehicle	Addition or deletion.					X	
Legal Name	New legal name.						X
	Deleting "Inc." from the legal name.						X
Mergers	Merger of two or more license holders to form a new legal entity.	X					
Acquisitions	Non license holder acquires all facilities from a license holder and continues to operate the acquired facilities using SOPs previously approved by FDA.	X (buyer)					X (seller)
	Non license holder acquires some but not all facilities from a license holder.	X (buyer)					X (seller)

APPENDIX B: REPORTING FACILITY CHANGES

FACILITY OPERATION	CHANGE PERFORMED	BLA Note: BLA is not a reporting category under 21 CFR 601.12	Reporting Category PAS	CBE30	CBE	AR	PC Note: Product correspondence is not a reporting category under 21 CFR 601.12
	License holder acquires facilities previously operating under the seller's U.S. license number that will operate under the buyer's U.S. license number.			X			
	Combining facilities operating under different licenses owned by the same corporation into one of the existing license number.			X			

APPENDIX C: REPORTING CHANGES IN FACILITY RELOCATIONS

FACILITY OPERATION	Reporting Category		
	PAS	CBE30	AR
Relocation of a facility where product manufacturing is performed and there are no changes in SOPs or major equipment but there are major changes in Core Personnel.	X		
Relocation of a facility where manufacturing is performed that result in a major change in SOPs, major equipment and Core Personnel.	X		
Relocation of a facility which in turn requires the manufacture to temporarily close so that new staff can be hired and trained.	X		
Relocation of a contractor that results in a change in SOPs and/or equipment.	X		
Relocation of a facility where product manufacturing is performed and there is no change in SOP or Core Personnel, but there is a change with respect to major equipment.		X	
Relocation of a product testing laboratory.	X		
Relocation of a facility where product manufacturing is performed and there is no change in SOP, major equipment or Core Personnel.			X

*Relocation of facilities: Changes in location must be submitted on Form FDA 2830 (Blood Establishment and Product Listing) (21 CFR 607.26) as an amendment to registration within 5 days of such change.

APPENDIX D: REPORTING CHANGES ASSOCIATED WITH BLOOD ESTABLISHMENT COMPUTER SOFTWARE (BECS)

	Reporting Category			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
BECS Used With the Donor Interview Process • **Internal access only:** Used only within the company and not remotely accessible by donors for completion of the DHQ. Such systems may be web-based (i.e., intranet), wireless, or hard-wired. • **External access by donors:** Remotely accessed by donors via internet for completion of the DHQ.				
A. Self-Administered Donor History Questionnaires (DHQ)				
1. Implementation of a 510(k) cleared BECS internally accessed for a computer-assisted interactive interview (CASI) software program with a DHQ:				
a. Not previously approved or accepted by FDA in guidance.	**X**			
b. Previously approved or accepted by FDA in guidance.		**X**		
2. Implementation of a 510(k) cleared BECS externally accessed by donors for a computer-assisted interactive interview (CASI) software program with a DHQ:				
a. Not previously approved or accepted by FDA in guidance.	**X**			
b. Previously approved or accepted by FDA in guidance.		**X**		
B. Staff-Administered and Documented DHQ				
1. Implementation of a 510(k) cleared BECS for administering a DHQ				
a. Not previously approved or accepted by FDA in guidance.	**X**			
b. Previously approved or accepted by FDA in guidance.		**X**		

APPENDIX D: REPORTING CHANGES ASSOCIATED WITH BLOOD ESTABLISHMENT COMPUTER SOFTWARE (BECS)

	Reporting Category			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
Other BECS Applications				
A. Initial implementation of 510(k) cleared BECS that interfaces with an apheresis device to permit bi-directional data flow impacting the operation of the apheresis device with regard to (not an all-inclusive list) sending eligible product combinations, donor information, and initial configuration information to the apheresis device and determining component eligibility based on the interval, frequency, non-rinse back events and RBC/Plasma loss from a donor's past donations.		**X**		
B. Implementation of a blood establishment computer system that is interfaced with an automated blood cell separator device as described in the 510(k) clearance for the software.	**X**			
C. Implementation of a blood establishment computer system that maintains data used by blood establishment personnel to make decisions regarding the eligibility of donors and the release of blood and blood components for transfusion or for further manufacture. **Note:** This does not include the use of a computer-assisted interactive interview software program for self-administering of a donor history questionnaire. Report the name of the software manufacturer and the name and version number of the software.				**X**
1. Implementation of data entry and retrieval or library database software systems;				**X**
2. Initial installation of commercially available or in-house developed BECS or installation of software upgrades, provided there are no major changes in SOPs. **Note**: This does not apply to BECS installations used for self-administered DHQ.				**X**
3. Implementation of a validated computer crossmatch system.				**X**

APPENDIX E: REPORTING CHANGES IN APHERESIS OPERATIONS AND AUTOMATED BLOOD SEPARATOR DEVICES

	Reporting Category			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
Change(s) from manufacturing an approved product by automated apheresis to manufacturing additional products collected at the same facility using the same apheresis instrument, for example Platelets Pheresis, single or double units of Red Blood Cells, Source Plasma, or Source Leukocytes.	**X**			
Manufacture of leukocytes reduced blood components using an automated blood cell separator new to your establishment and you are not making the change under an approved CP.	**X**			
Conversion from manual to automated collection of Platelets, Plasma (including Source Plasma), Red Blood Cells and Source Leukocytes.	**X**			
Change in the manufacturer or model of automated apheresis equipment used in the collection of Red Blood Cells, Plasma (other than Source Plasma) or Platelets.	**X**			
Collection of plasma for transfusion as part of an approved apheresis program provided the applicant is otherwise approved to manufacture the plasma product. **Note:** This does not include Source Plasma.		**X**		
Changes or upgrades in automated apheresis equipment for example: Software changes that may have a moderate potential to have an adverse effect on the safety or effectiveness of the product.		**X**		
Changes or upgrades by the device manufacturer of automated apheresis equipment that does not affect the safety, purity or potency of the product(s), if the facility is already approved for the original procedure.				**X**
Changes or upgrades in automated apheresis equipment that result in a decrease in donation time.				**X**
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 leukocyte reduction procedure, and collection of an additional or different product.	**X**			

APPENDIX F: REPORTING CHANGES IN SOURCE PLASMA/IMMUNIZATION PROGRAMS FOR SOURCE PLASMA DONORS

	Reporting Category			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
Implementation of a new immunization program for Red Blood Cells or vaccines.	**X**			
Implementation of a vaccine hyperimmunization collection program in which the licensed vaccine is administered differently from the listed immunization schedule in the package insert, such as by dose or route of administration, and is not an alternative immunization schedule that has been approved by FDA.	**X**			
Collection of Source Plasma from disease-state or high-risk donors.	**X**			
Implementation of a vaccine hyperimmunization collection program in which the licensed vaccine administration schedule is consistent with the immunization schedule listed in the package insert or where CBER has approved an alternate immunization schedule, such as by dose or route of injection.		**X**		
Change in the manufacturer of a licensed vaccine previously used in an approved vaccine hyperimmunization program if the injection protocol of the new package insert is different from procedures in the previously approved SOP.		**X**		
Collection of Source Plasma from donors with pre-existing disease-associated, Red Blood Cell and/or HLA antibodies, if previously approved for a Source Plasma Collection Program (Ref. 10). Submit labels for this program under 21 CFR 601.12(f)(2).				**X**
Changes in manufacturer of a licensed vaccine previously used in an approved vaccine hyperimmunization program, if the vaccine is administered according to the package insert and the package insert is consistent with the currently approved SOP.				**X**
Discontinuation of the manufacture of Source Plasma.				**X**
Request for an exception or alternative procedure to 21 CFR 640.62 under 21 CFR 640.120 to implement a physician substitute program.	**X**			
Implementation of a hyperimmunization program previously approved by CBER for licensed vaccines at additional facilities.		**X**		

APPENDIX G: REPORTING CHANGES IN THE MANUFACTURE OF LEUKOCYTES REDUCED BLOOD COMPONENTS

	Reporting Category			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
Manufacture of leukocytes reduced blood components at a facility other than the one named under an approved CP.	**X**			
Manufacture of leukocytes reduced blood components when you intend to change your manufacturing process in a manner that presents a substantial potential to have an adverse effect on the safety or effectiveness of the product.	**X**			
Manufacture of leukocytes reduced blood components using an automated blood cell separator new to your establishment and you are not making this change under an approved CP.	**X**			
Change from one type of FDA approved or cleared leukocyte reduction filter to another type of FDA approved or cleared leukocyte reduction filter.				**X**
Software and hardware upgrades to the leukocyte reduction process for apheresis collection that may have a moderate potential to have an adverse effect on the safety or effectiveness of the product(s).		**X**		

APPENDIX H: REPORTING CONTRACT CHANGES

	Reporting Category			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
Use of an FDA registered contract facility not previously engaged in blood product testing to perform routine serologic testing and/or infectious disease screening, and supplemental and/or confirmatory testing for blood and blood products. These contract facilities perform the tests of record (tests used to determine donor eligibility/product suitability).	**X**			
Use of a contract facility that was not previously engaged in performing a manufacturing step on blood products to perform a manufacturing step. This includes, but is not limited to, contract facilities that irradiate blood products or supply Red Blood Cells for immunization.	**X**			
Expanding operations to include infectious disease test laboratories. **Note:** Refer to Appendix B for reporting facility changes and Appendix C for handling changes in facility relocations.	**X**			
Use of an FDA registered off-site contract storage facility to store an unlicensed product collected under a pending supplement or for the storage of excess licensed product that meets all product release criteria.		**X**		
Use of an FDA registered contract facility currently engaged in performing manufacturing steps on blood products, to perform a specific manufacturing step.			**X**	
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. **Note:** This does not include a change in a contract testing laboratory that performs the infectious disease or ABO/Rh tests of record. Such a change must be reported as a CBE. See sections IV.B. and C. of this guidance.				**X**

APPENDIX H: REPORTING CONTRACT CHANGES

	Reporting Category			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
Changes in infectious disease tests that are required or recommended by FDA at a previously approved contract testing laboratory. For example: adding an FDA required or recommended test to the testing currently performed by the approved contract testing laboratory.				**X**
Notification of changes in operations made by an approved contractor, for example, notification by an approved contract testing laboratory that they have changed the contract laboratory they use to perform confirmatory testing**.**				**X**
Temporary use of a previously approved alternate or back-up contractor to perform a manufacturing step. Include the dates the alternate contractor was used.				**X**
Use of, or change in, a contractor to provide personnel responsible for collecting blood products or performing quality assurance activities.				**X**
Change in address of any unlicensed contractor**.**				**X**

APPENDIX I: REPORTING CHANGES IN DONOR HISTORY QUESTIONNAIRES

	Reporting Category			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
Implementation of a donor history questionnaire or associated procedures that differ from, and are less restrictive than the FDA-accepted donor history questionnaire and accompanying materials, manufacturer's directions or recommendations described in FDA guidance documents.	**X**			
Implementation of an abbreviated self-administered donor history questionnaire using the written form or audio/visual presentation methods described in the acceptable aDHQ documents for repeat or frequent donors (Ref. 15).				**X**
Implementation of the acceptable donor history questionnaire and accompanying materials, if used <u>without</u> modification or if modifications are <u>more</u> restrictive (Ref. 16).				**X**
Implementation of the acceptable aDHQ documents using a computer-assisted interactive interview procedure.		**X**		

APPENDIX J: REPORTING CHANGES IN STANDARD OPERATING PROCEURES (SOPS)	**Reporting Category**			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
Addition or revision of SOP(s) for the following manufacturing categories if the change is less restrictive than the procedure(s) described in previously approved SOP(s) or is not addressed in guidance document(s): a. Donor eligibility, including donor deferral; b. Blood collection and processing, including use of a product for preparing the donor's arm prior to donation when the product is not labeled as a surgical or donor scrub; c. High-risk behavior questions/AIDS information; d. Donor history questionnaire forms (including informed consent); e. Blood and blood component manufacturing for licensed products; and f. Quarantine and disposition of unsuitable products. **Note:** Report changes in the content of the procedure or form. Do not report formatting or minor changes to SOPs and forms. You may reference previously approved SOPs and forms. When referencing a previously approved SOP or form, please include the FDA application or supplement tracking number.	**X**			
Implementation of an SOP to contact donors within 24 hours of the time of collection for obtaining or clarifying a donor's response to the donor history questionnaire after the donor has left the collection establishment (Ref. 17). **Note:** This does not include obtaining missing pre-collection vital signs and hemoglobin/hematocrit determinations after donation.	**X**			
Implementation of an SOP for shipping inadvertently collected blood and blood components that are repeatedly reactive or positive for an infectious disease agent and are to be used in the further manufacture of noninjectables (21 CFR 610.40(h)(2)(ii)(A)).	**X**			

APPENDIX J: REPORTING CHANGES IN STANDARD OPERATING PROCEURES (SOPS)	**Reporting Category**			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
Revision of an SOP for the following categories if the change is more restrictive than previously recommended or described in published FDA guidance documents. a. Donor eligibility, including donor deferral, for example, deferring donors who are at risk for Lyme disease; b. Use of a product for the preparation of a donor's arm prior to donation, when the product is labeled as a surgical or donor scrub; c. High-risk behavior questions/AIDS information; d. Donor history questionnaire forms (including informed consent); e. Blood and blood component manufacturing for licensed products only; and f. Quarantine and disposition of unsuitable products.				**X**
Implementation of additional procedures or tests that are not required or recommended by FDA and which do not conflict with FDA requirements or recommendations. If the test or procedure is included in the informed consent form, the form should not contain any exculpatory language or claims about the procedure or test.				**X**
Discontinuation of procedures no longer required or recommended by FDA.				**X**
Implementation of another licensed manufacturer's FDA approved SOP, with written permission from the licensed manufacturer.				**X**
Revision of SOP for determining donor eligibility to allow individuals who have had a tattoo or body piercing in the previous 12 months to donate, if the tattoo or body piercing was applied by a state regulated entity with sterile needles and non-reused ink or single-use equipment.				**X**
Changes in the quality control method if the quality control 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, and supplies.				**X**

APPENDIX J: REPORTING CHANGES IN STANDARD OPERATING PROCEURES (SOPS)	**Reporting Category**			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
Implementation of additional infectious disease tests that are required or recommended by FDA, if directed by the relevant guidance document to report implementation in this manner.				**X**

APPENDIX K: REPORTING CHANGES IN EQUIPMENT

	Reporting Category			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
Use of a 510(k) cleared automated device for separating Whole Blood into Red Blood Cells and Plasma.		**X**		
Implementation of a computer system that is interfaced with an automated blood cell separator device as described in the 510(k) clearance for the software.		**X**		
Change in irradiation equipment used by you or your contractor, for example, from gamma irradiator to linear accelerator, or to a gamma irradiator by another manufacturer or to an x-ray irradiator.				**X**
Changes in infectious disease screening testing methods if the procedures are consistent with manufacturer's directions.				**X**
Changes in equipment that performs total protein and serum/plasma protein electrophoresis on donor specimens.				**X**
Changes in equipment that performs vital signs testing (for example, pulse, blood pressure, temperature) and hemoglobin/hematocrit testing on blood donors or donor specimens.				**X**
Use of sterile connecting (docking) device to manipulate product in a sterile manner (for example, 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.				**X**
Changes or upgrades in equipment used for performing product quality control testing, including White Blood Cell and platelet counts.				**X**
Changes or upgrades in equipment used to perform platelet counts on donor samples.				**X**
Implementation of FDA-cleared or approved automated equipment to perform ABO/Rh testing, syphilis, and infectious disease screening testing on donor samples.				**X**

APPENDIX L: REPORTING PRODUCT MANUFACTURING/PROCEDURAL CHANGES

	Reporting Category			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
Implementation of a new manufacturing process, including, but not limited to: • Leukocyte reduction of blood components; • Irradiation; • Freezing/deglycerolizing; • Rejuvenating; • Washing; • Testing for communicable diseases; • Pre-storage pooling of Platelets; • Pre-storage pooling of Cryoprecipitated AHF; • Automated apheresis collections; and • Manufacture of Whole Blood derived Platelets.	**X**			
Request for approval of a Comparability Protocol (CP) (21 CFR 601.12(e)).	**X**			
Request for an exception or alternative procedure under 21 CFR 640.120, for which there is no published guidance.	**X**			
Request for an exception or an alternative procedure under 21 CFR 640.120 for which published guidance is available and implementation conforms to the guidance, for example, implementation of an infrequent plasmapheresis donor collection program that is consistent with FDA's guidance for this program.		**X**		
Implementation of an approved anti-HIV 1/2 test that includes detection of antibodies to HIV-1 Group O (Ref. 18).				**X**
Changes in Whole Blood collection sets or leukocyte reduction filters for products prepared from Whole Blood, if used according to manufacturer's instructions.				**X**
Statistical Sampling Plans for Validation and/or Quality Control: • Implementation of new or revised procedures containing a statistical sampling plan that has not been previously delineated in FDA guidance.	**X**			
• Implementation of new or revised procedures containing a statistical sampling plan that has been delineated in FDA guidance.	**X**			

APPENDIX L: REPORTING PRODUCT MANUFACTURING/PROCEDURAL CHANGES

	Reporting Category			
Type of Change	**PAS**	**CBE30**	**CBE**	**AR**
• Revision of previously approved sampling plan procedures in accordance with recommendations in guidance in the following cases: o Change the sample size in a previously approved hypergeometric sampling plan procedure in accordance with FDA guidance recommendations to allow for changes in collections or product manufacturing numbers. o Change the sample size in a previously approved binomial or hypergeometric sampling plan procedure with regard to the number of allowable failures; e.g., change from a sample size with 0 failures to a sample size with 1 failure or vice versa.				**X**