Plasma Protein Therapeutics Association

August 29, 2013
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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

SUBJECT: Draft Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture
[Docket No. FDA—1999—D---3528 (Formerly Docket No. 99D—5046)]

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) thanks FDA for the opportunity to participate in the guidance development process and is pleased to provide these comments on the Draft Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture (June 2013).[1] PPTA understands that the Draft Guidance provides manufacturers of licensed Whole Blood and blood components intended for further manufacture, including Source Plasma, with recommendations (1) intended to assist with determining which reporting mechanism is appropriate for submission of changes to an approved biologics license application in accordance with the requirements under 21 CFR 601.12 and (2) 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). PPTA also understands that the Draft Guidance, when finalized, is intended to supersede the document of the same title (July 2001). [2]

PPTA agrees with FDA that, when a manufacturer of licensed biological product determines that it is appropriate to make a change in its product, production process, quality controls, equipment, facilities, responsible personnel, or labeling as documented in its approved application, 21 CFR 601.12 states the requirements to report such changes to the Agency. PPTA appreciates FDA's efforts to revise the recommendations in the 2001 Guidance for certain changes to an approved application based on the experience gained over the last decade.

About PPTA

PPTA is the international trade association and standards-setting organization for the world's major collectors of Source Plasma and manufacturers of plasma-derived products and recombinant analogues, collectively referred to as plasma protein therapies, which are used in the treatment of a number of rare diseases. These diseases are often genetic, chronic, life-threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. Plasma protein therapies include clotting-factor

[1] *See* FR Notice, 78 Fed. Reg. 32668-69 (May 31, 2013)
[2] *See id.*at 32668

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therapies for individuals with hemophilia A and B and other bleeding disorders; immunoglobulins to treat a complex of diseases in individuals with immune deficiencies; therapies for individuals who have alpha-1 anti-trypsin deficiency, which typically manifests as adult onset emphysema and limits substantially life expectancy; and albumin, which is used in emergency-room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

General Comments

The proposed revision of this important guidance document and the opportunity to comment on the proposed revisions is much appreciated. This document provides guidance regarding the reporting of specific changes to the manufacturing process for blood and blood components, and helps to correctly classify changes into the broad categories as stated in 21 CFR 601.12. Industry routinely uses this guidance document when evaluating proposed changes to manufacturing processes. This guidance document provides the information that allows proposed changes to be reported in the proper category.

Comparing the recommendations in the 2001 version of this guidance document with the recommendations in the 2013 draft of this guidance document suggests that the determination of the correct reporting category for proposed changes has become increasingly complex. Specific comments in this document will illustrate some of this complexity, due in part to the increased use of sophisticated systems in the manufacturing process for blood and blood components.

To help industry deal with the increased complexity and to properly classify proposed changes for reporting purposes, a moderate reorganization of the guidance document will be suggested. The suggested reorganization, and the standardization and clarification that would result, would greatly improve the utility of this very important document that is consulted on an almost daily basis by industry. It is strongly recommended that the draft guidance be revised and republished for comment.

Comments are presented under the following headings:

1) Document Organization and Format
2) Terminology
3) References to Other Guidance Documents
4) Specific Comments Related to Document Content
5) Table of Contents

1) Document Organization and Format

The 2013 draft guidance document maintains the organization of the 2001 guidance document in that it is organized primarily by reporting category (PAS, CBE-30, etc.) with examples of specific changes that represent current thinking inserted into each reporting category. This approach was perhaps more appropriate for the first version of this document, but FDA's experience with applying a risk-based approach to the regulation of the blood industry (very much appreciated) should be a driver in the evolution of this document.

The utility of the guidance document could be improved by revising the existing sections of the document that describe each reporting category to include high-level suggestions for how to perform a risk analysis, or perhaps an algorithm that could be used to determine whether the proposed change has a substantial, moderate or minimal potential to adversely affect the safety or effectiveness of the product. An example of the analysis of changes that are classified into each category could be included. Interactions with FDA over the past several years have provided a plethora of concrete examples of the sensible application of these principles. A high-level description of the principles and approach used for these analyses would be useful to industry and may foster more efficient and effective discussions with FDA regarding proposed changes, and also increase reporting of proposed changes in the correct reporting category.

Rather than inserting all of the specific examples of changes into the introductory section that describes each reporting category, the guidance document could contain a series of appendices (similar to the appendices already included), that would list specific changes by the type of change and then show the proper reporting categories. This format would eliminate the need to review each reporting category in order to identify the best fit for the proposed change, which can be tedious, since the best fit can be determined only after all the possible choices have been reviewed.

The following detailed example of entries related to Blood Establishment Computer Software (BECS) will help to illustrate this suggestion. Changes to BECS are included in the PAS, CBE-30 and AR sections of the draft guidance. The list shows the complexity and the difficulty of selecting the correct reporting category using the descriptions as currently written.

PAS:

- Implementation of a non-web-based computer-assisted interactive interview software program for a new donor history questionnaire not previously reviewed and accepted by FDA in guidance. (p. 10)

CBE-30:

- Implementation of 510(k) cleared non-web-based and/or web-based Blood Establishment Computer Software (BECS) for self-administering a donor history questionnaire (DHQ) that was either previously accepted by FDA in guidance or approved by FDA for use by the applicant. (p. 14)
- Initial installation 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. (p. 15)
- 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. (p. 14)

AR:

- 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.
    - You should include the following in the AR:
        - *i*. Implementation of data entry and retrieval or library database software systems;
        - *ii.* 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.
        - *iii.* Implementation of a validated computer crossmatch system; and
        - *iv.* Implementation of software that allows establishment personnel to administer the DHQ to the donor and to document donor eligibility. (p. 19 - 20)
- Implementation of software for the donor history questions where staff administers the questions verbally and documents the donor's responses electronically. (p. 19)

As previously mentioned, the user would have to read numerous examples (including many non-BECS related changes) on pages 10 to 20 of the document to identify the best fit for the proposed change. It would be far easier to select the best fit by reviewing a table showing each type of change related to BECS. See the following table for an example.

Changes to Blood Establishment Computer Software and/or Systems*		**Reporting Category**					
Type of Change	**Example(s)**	**New BLA**	**PAS**	**CBE30**	**CBE**	**AR**	**PC**
Implementation of a non-web-based computer-assisted interactive interview software program for a new donor history questionnaire not previously reviewed and accepted by FDA in guidance. (p. 10)	*(insert examples here)*		x				
Implementation of 510(k) cleared non-web-based and/or web-based Blood Establishment Computer Software (BECS) for self-administering a donor history questionnaire (DHQ) that was either previously accepted by FDA in guidance or approved by FDA for use by the applicant. (p. 14)	*(insert examples here)*			x			
Initial installation of 510(k) cleared BECS that interfaces with an apheresis device to permit bi-directional data flow impacting the operation of the	*(insert examples here)*			x			

Changes to Blood Establishment Computer Software and/or Systems*		**Reporting Category**					
Type of Change	**Example(s)**	**New BLA**	**PAS**	**CBE30**	**CBE**	**AR**	**PC**
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. (p. 15)							
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. (p. 14)	*(insert examples here)*			x			
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. (p.19)	*(insert examples here)*					x	
i. Implementation of data entry and retrieval or library database software systems; (p.19)	*(insert examples here)*					x	
ii. Initial installation of commercially available or in-house developed BECS or	*(insert examples here)*					x	

Changes to Blood Establishment Computer Software and/or Systems*		**Reporting Category**					
Type of Change	**Example(s)**	**New BLA**	**PAS**	**CBE30**	**CBE**	**AR**	**PC**
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. (p. 19)							
iii. Implementation of a validated computer crossmatch system (p. 20)	*(insert examples here)*					x	
iv. Implementation of software that allows establishment personnel to administer the DHQ to the donor and to document donor eligibility. (p. 20)	*(insert examples here)*					x	
Implementation of software for the donor history questions where staff administers the questions verbally and documents the donor's responses electronically. (p. 19)	*(insert examples here)*					x	

* Note: The example suggests a format only. No clarification of the types of changes has been attempted.

An additional advantage to the organizational format illustrated by the table is that when the changes related to BECS are reviewed as a consolidated list, additional opportunities for clarification and standardization become evident. For example, it is difficult to determine if the inclusion (or not) of "510(k) cleared" is intentional or significant in the different descriptions of changes to BECS. The descriptions of the types of changes could be improved by simplifying the wording such that the change is mutually exclusive, thereby facilitating the selection of the proper category.

In another example, the changes described in the last two rows of the table appear to be the same. Although both are examples of AR changes and selection of either one would result in the correct reporting category, this is an example of two choices that are not mutually exclusive.

The listing in the table also reveals the use of varying terminology, e.g., apheresis device and automated blood cell separator device, initial installation and implementation, etc.

As already mentioned, the proposed formatting is consistent with the formatting of the new Appendices in the draft guidance. A column has been inserted to allow for the inclusion of specific examples that could assist the user in correctly classifying the proposed change. In

addition, the rightmost column in the table is for Product Correspondence. It is recommended that Product Correspondence be included in the guidance document as a fifth reporting category for proposed changes. The draft guidance document already includes changes in the corporate mailing address and changes in authorized officials as two types of changes that should be reported as Product Correspondence, and Appendix B lists several changes that should be reported as Product Correspondence.

Additionally, it is recommended that BECS be included in the list of definitions, especially since BECS refers to Blood Establishment Computer Software and not to Blood Establishment Computer System.

Changes to computer systems could also include hardware that is not considered BECS (software) and appropriate change categories.

Other types of changes (not all inclusive) that would benefit from being provided as a tabular list of clearly and succinctly described mutually exclusive options would include:

- Changes in apheresis programs and/or automated blood cell separator devices
- Immunization programs for Source Plasma donors
- Changes in the manufacture of leukocytes reduced blood components
- Changes in donor testing and testing laboratories

To summarize, it is recommended that the guidance document include a brief description of the various reporting categories, guidance on an appropriate risk analysis, examples of specific changes and the correct reporting category in tabular format. This format would:

a. Acknowledge and address how end users use the guidance document (i.e., if the user has a change in mind, not a reporting category)
b. Facilitate comparison and selection of reporting categories within a single change type by grouping related changes (e.g., change to a BECS)
c. Facilitate consistency in terminology used in the guidance document
d. Improve access to the information in the guidance document
e. Facilitate revision of the guidance document, i.e., as current thinking changes the specific entries in the appropriate tables could be easily updated. (See comments under References to Other Guidance Documents, below.)

2) Terminology

As already mentioned, terminology used in the June 2013 Draft Guidance is often inconsistent, and it is not always clear what is the intended meaning, which sector of the industry, i.e., blood products for transfusion or Source Plasma, and to which processes certain guidance applies. It is recommended that terminology be standardized and, where appropriate, definitions and synonyms be added to the Definitions section of the document.

Some specific examples are presented below:

- **Automated blood cell separator device**
  The following terms are all used to describe an automated blood cell separator device (which is believed to be the proper term):
  - Automated apheresis instrument (IV.A.1.f)
  - Automated apheresis equipment (IV.A.2.b, IV.A.2.c, IV.B.2.c, IV.D.2.a, IV.D.2.j)

- Automated blood cell separator (IV.A.1.q, IV.A.4.a.i)
- Automated blood cell separator device (IV.B.2.b)
- Automated plasma-only apheresis equipment (IV.D.2.m)
- Apheresis device (IV.B.2.e)
- 510(k) cleared device for separating Whole Blood into Red Blood Cells and Plasma (IV.B.2.a.)

- **Donor testing**

  The term, donor testing, is a broad term that can refer to a variety of testing activities (e.g., vital signs testing, hemoglobin / hematocrit testing, total protein testing, serum/plasma protein electrophoresis, blood typing, antibody screening, and communicable disease testing). For clarification, a definition of donor testing and/or references to specific testing is needed in the guidance document.

  (See also: Comments Related to Specific Statement in the Guidance Document, Comments 6 and 9.)

- **Whole Blood and blood components** (D.4.b., D.6.c.)

  The phrase "Whole Blood and blood components" sometimes appears alone, as in the definition of Manufacturer's Instructions, and sometimes appears followed by "including Source Plasma", as it does in the definition of Establishment / Facility. As a result, the absence of "including Source Plasma" can be interpreted to mean that the guidance does not apply to Source Plasma (e.g., IV.D.4.a, IV.D.6.c). It is recommended that the meaning of "Whole Blood and blood components" be defined in the guidance document and that the terminology used be consistent throughout so that it is clear when guidance applies to manufacturers of Source Plasma.

This draft guidance document continues the trend of using terminology described in the proposed rule, "Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use" [Docket No. 2006N-0221] published in the Federal Register: November 8, 2007 (Volume 72, Number 216), and thus introduces inconsistencies with the terminology of the CFR. The standardization of the terminology used in the CFR and guidance documents that will result with the publication of the final rule is anxiously awaited.

3) <u>References to Other Guidance Documents</u>

This draft guidance document contains references to other guidance documents and also provides updates to information that is contained in other guidance documents. This practice makes it difficult to find the most current recommendations on a given topic.

For example, this guidance provides updated information regarding donor eligibility after having received a tattoo. While publication of this current thinking is much appreciated, this information would more appropriately be included in a guidance document that discusses donor eligibility.

As another example, the November 2010, "Guidance for Industry: Recommendations for Blood Establishments: Training of Back-Up Personnel, Assessment of Blood Donor Suitability and Reporting Certain Changes to an Approved Application," communicated a change in the reporting category (from CBE-30 to CBE) for changes related to the use of contractors and

implementation of self-administered donor questionnaire with respect to high-risk behavior questions. These changes have been included in the 2013 draft guidance, but for the period of time until inclusion in the appropriate guidance document, industry had to remember that the update to the reporting category was contained in a separate guidance document. An advantage to listing the examples of changes in appendices to this guidance document would be that changes such as the above mentioned change could easily be communicated by updating the appropriate appendix in this guidance document. This concept could be expanded so that guidance for reporting changes would not be included in the specific guidance documents, but would rather refer to this guidance document. As specific guidance documents are issued, information regarding the reporting of the change could be added to the appropriate appendix, which could be made available simultaneously with the specific guidance document. Industry would then only have to look in one guidance document to see the current thinking regarding the reporting of any and all changes. This would simplify the process for industry, and could result in improved compliance with reporting requirements.

Other examples of complex cross references are cited in the following section, e.g., Comments 22, 27, 28 and 29.

4) <u>Specific Comments Related to Document Content</u>

The following tables contain specific comments for consideration.

Section II. Background		
Number	**Reference**	**Comment**
1	**B. Moderate Change** p. 2	CBE30 is presented as the default reporting category for changes with a moderate potential to have an adverse effect on the safety or effectiveness of the product. The note states, *"…FDA may determine that the product made using the change may be distributed immediately upon receipt as a Changes Being Effected Supplement (CBE)."* It is of limited value to the manufacturer to learn after a CBE30 supplement has been submitted that it could have been submitted as a CBE supplement. Therefore, it is recommended that a note be added to encourage manufacturers to consult with FDA prior to submitting a CBE30 to determine whether or not the submission should be a CBE30 or CBE supplement. (See also: Comment 18.)

Section III. Definitions		
Number	**Reference**	**Comment**
2	**CBE (Changes Being Effected Supplement)** p. 4	The definition of CBE includes, *"Note: This supplement must be labeled "Supplement – Changes Being Effected."* It is recommended that this note be removed. The content of the note is instruction, not part of the definition. This instruction should be moved to Section IV.C.

Section III. Definitions		
Number	**Reference**	**Comment**
3	**CBE30 (Changes Being Effected in 30 Days Supplement)** p. 4	The definition of CBE30 includes, *"Note: This supplement must be labeled "Supplement – Changes Being Effected in 30 Days."* It is recommended that the note be removed. The content of the note is instruction, not part of the definition. This instruction should be moved to Section IV.B.
4	**Comparability Protocol (CP)** p. 5	The definition of Comparability Protocol includes the phrase, *"…and which may be referred to as a "Comparability Protocol" supplement."* The meaning of the word "may" is unclear. It is recommended that the phrase be revised so that it is clear whether it is optional or required to further identify a PAS that contains a comparability protocol as a "Comparability Protocol" supplement.
5	**Establishment / Facility Types of Facilities: Distribution Center** p. 6	The facilities included in this listing should be harmonized with the list of facilities included on the Form FDA 2830, Blood Establishment Registration and Product Listing, and listed in Appendix A. Definitions should be clarified to ensure mutual exclusivity, in order to facilitate the quick and easy classification of a facility for which a change is planned and to facilitate proper registration of the facility. The following is a listing of facilities on Form FDA 2830: ▪ Community (Non-Hospital) Blood Bank ▪ Hospital Blood Bank ▪ Plasmapheresis Center ▪ Product Testing Laboratory ▪ Hospital Transfusion Service ▪ Component Preparation Facility ▪ Collection Facility ▪ Distribution Center ▪ Broker/Warehouse As an example of potentially useful clarifications, the definition of a Distribution Center in the draft guidance document seems to also include a Broker/Warehouse. The definitions of a Component Preparation Facility and a Distribution Center should also be clarified regarding the distribution of blood products for transfusion. The use of simple bulleted lists is recommended to add clarity to some of the definitions.
6	**Establishment / Facility Types of Facilities: Plasmapheresis Center** p. 6	The definition of Plasmapheresis Center includes, *"Plasmapheresis centers may also perform FDA required or recommended donor testing."* The inclusion of "*perform FDA required or recommended donor testing*" is confusing. This phrase should either be deleted or clarification regarding what is meant by "donor testing" added. This could be done by defining this phrase in this sentence or by adding

Section III. Definitions		
Number	**Reference**	**Comment**
		Donor Testing to the Definitions section. As currently stated, it is unclear if "donor testing" includes only testing for communicable disease agents and diseases (not likely to be performed in a plasmapheresis center), or if it includes testing done to determine donor eligibility, e.g., hematocrit and total protein, both of which are required prior to donation and therefore not optional.
7	**Product Correspondence** p. 8	The definition of Product Correspondence includes the note: *"Product correspondence does not usually require a response from FDA."* Clarification is requested regarding the note. PPTA understands that CBER staff have indicated that a Submission Tracking Number (STN) will be assigned to Product Correspondence going forward. This change is appreciated since it will confirm that the Product Correspondence has been received and placed in the license file. As previously mentioned, and as will be reiterated in Comment 44, it is recommended that Product Correspondence be included in this guidance as a reporting category for certain proposed changes. The draft guidance document includes changes in the corporate mailing address and changes in authorized officials as two types of changes that should be reported as Product Correspondence, and Appendix B lists several changes that are to be reported as Product Correspondence. In addition, eSubmitter should be updated for submission of a product correspondence through this system. The information in eSubmitter is built on previous submissions and when a document is submitted outside the system, references to it in future submissions must be made using text in comment fields.

Section IV. Recommendations		
Number	**Reference**	**Comment**
8	**A. Changes Requiring Supplement Submission and Approval Prior to Distribution of the Product Made Using the Change (Major Changes) (PAS)**	The last sentence on page 8 states, *"Labeling changes requiring submission in a PAS are described in 21 CFR 601.12(f)(1)."* It is recommended that this sentence be removed, as it is redundant. An equivalent sentence appears on page 9. It is further recommended that equivalent guidance regarding labeling be added to the sections in the guidance that pertain to CBE30 supplements and Annual Reports.

Section IV. Recommendations		
Number	**Reference**	**Comment**
	p. 8	
9	**A. PAS** p. 9 1.a.vi	The phrase, *"Testing for communicable diseases,"* appears in the list of manufacturing/procedural changes that require a PAS. As already mentioned under Terminology, it is recommended that the language used to describe testing be defined and standardized throughout the guidance document.
10	**A. PAS** p. 10 1.b	On page 10, 1.b contains a list of six categories of SOP changes that require a PAS if the change is less restrictive than the procedure(s) described in previously approved SOP(s) or is not addressed in guidance document(s). The six categories are not clearly delineated; there is overlap among them. For example, "Donor eligibility" is listed in item 1.b.i, while "donor history questionnaire forms" is listed in item 1.b.iv. Donor history questionnaires are used to assist in determining donor eligibility. Similarly, "blood and blood component manufacturing" is listed in item 1.b.v, while "blood collection and processing" is listed in item 1.b.ii. Blood collection and processing are steps in blood and blood component manufacturing. It is recommended that the categories be more clearly delineated, and include as appropriate, the manufacturing steps included in the definition of "manufacture" on page 7.
11	**A. PAS** pp. 10 – 11 1.c – 1.r	The examples provided on pages 10 and 11 of specific changes are not grouped by topic. As already mentioned, it is recommended that all the examples of specific changes be grouped by topic (e.g., manufacture of leukocyte reduced blood components). Such a listing might address that some of the specific changes actually are examples of the changes listed in Section 1b., and therefore could be included as specific examples under 1b. For example, 1.c., 1.d., and 1.e., all appear to be examples of 1.b.iv, Donor history questionnaire forms. (See also: Document Organization and Format.)
12	**A. PAS** p. 10 1.g (also p. 14, 1.b)	Under Product Manufacturing/Procedural Changes, item 1.g, *"Addition of an immunization program for Red Blood Cells or licensed vaccines,"* is listed as a change that requires submission of a Prior Approval Supplement. On page 14, a similar change is described as a change that requires a CBE30 supplement: *"Implementation of a hyperimmunization program for licensed vaccines where the program is consistent with the*

Section IV. Recommendations		
Number	**Reference**	**Comment**
		immunization schedule listed in the package insert or where CBER has approved an alternate immunization schedule, such as by done or route of injection." The differences between these two options are not clear. Clarification of the descriptions, and the addition of concrete examples, would be beneficial. (See also: Documentation Organization and Format.)
13	**A. PAS** p. 11 1.i; (also p. 14, 1.e)	Several of the examples are related to the submission of a request for an exception or alternative procedure under 21 CFR 640.120. For example, on page 11, item 1.i states, *"Request for an exception or alternative procedure to 21 CFR 640.62 under 21 CFR 640.120 to implement a physician substitute program."* Item 1.l states, *"Request for an exception or alternative procedure under 21 CFR 640.120, for which there is no published guidance."* Similarly, on page 14, item 1.e states, *"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."* These are specific examples of where it is appropriate to submit a request for an exception or alternative procedure under 21 CFR 640.120, but 21 CFR 640.120 may be used for exceptions or alternative procedures for a variety of reasons. It is recommended that a section be added to the guidance document that groups these changes and provides more detailed guidance on the submission of a request for an exception or alternative procedure under 21 CFR 640.120.
14	**A. PAS** p. 12 2.c	Under Equipment Changes that require a PAS, item 2.c. states, *"Change in the manufacturer or model of automated apheresis equipment used in the collection of Red Blood Cells, Plasma or Platelets."* "Plasma" has been added with this draft version of the guidance. In this entry, it is not clear whether "Plasma" includes Source Plasma. PPTA wants to confirm that this does not include Source Plasma. A similar entry appears in the Annual Reports section of the guidance where item 2.m. states that the following change may be reported in the Annual Report: *"Change in manufacturer of automated plasma-only apheresis equipment."* Clarification is needed. It should include upgrades to equipment (e.g., PCS to PSC2 or Auto-C to Aurora). (See also: Documentation Organization and Format; Terminology.)

Section IV. Recommendations		
Number	**Reference**	**Comment**
15	**A. PAS** p. 12 3.b	Under Contractor Changes that require a PAS, item 3.b. begins, *"Use of a contract facility that was not previously engaged in performing a manufacturing step...",* while Item 3.a includes the phrase "a FDA registered contract facility." It is recommended that this phrase also be added to 3.b. for clarity.
16	**A. PAS** p. 12 4.a.ii	Under Facility Changes that require a PAS, item 4.a.ii states, *"Additional Source Plasma centers under an approved license."* Clarification is needed. It is not clear whether "additional" means new centers, only, or also includes re-opening or relocation of closed centers.
17	**A. PAS** p. 13 4.b	The note ends with the phrase, *"…and Appendix C for handling changes in facility relocations."* The words, "changes in" should be removed.
18	**B. Changes Requiring Supplement Submission at Least 30 Days Prior to Distribution of the Product Made Using the Change (Moderate Changes) (CBE30)** p. 13	The opening paragraphs of this section include the statements: *"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."* *"…we recommend that you have a mechanism to track the date we received the supplement submission…"* *"…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."* As this wording indicates, the potential consequences of reporting a change as a CBE30, and then finding out that the change should have been reported as a PAS can be severe, including the potential to recall product. It would be helpful if manufacturers were notified within 30 days that the CBE30 supplement was received and was reported in the correct category. This could be accomplished by sending the manufacturer the letter with the Submission Tracking Number (STN), within 30 days of receipt of the supplement (which is often FDA's practice).
19	**B. CBE30** p. 14 1.d	Under CBE30 Product Manufacturing/Procedural Changes, item 1.d. states, *"Implementation of 510(k) cleared non-web-based and/or web-based Blood Establishment Computer Software (BECS) for self-administering a donor history questionnaire (DHQ) that was either previously accepted by FDA in guidance or approved by FDA for use by the applicant."* It is not clear whether the word "that" in the clause "that was either previously accepted by FDA in guidance or approved by FDA for use by the applicant" refers to the BECS or to the DHQ. If it refers to the BECS, it is recommended that the phrase "or approved by FDA for use by the applicant" be removed, because the CBE30 supplement would

Section IV. Recommendations		
Number	**Reference**	**Comment**
		not be needed if approval had already been granted by the FDA for use by the applicant. If the phrase "approved by FDA for use by the applicant" refers to the FDA's approval for use of the DHQ as a manual process, the CBE-30 supplement required by this section would be for the use of the BECS for the administration of the already approved DHQ. Clarification is needed.
20	**B. CBE30** p. 14 1.d	Under CBE30 Equipment Changes, item 2.a. states, *"Use of a 510(k) cleared automated device for separating Whole Blood into Red Blood Cells and Plasma."* However, under PAS Equipment Changes, item 2.c. states, *"Change in manufacturer or model of automated apheresis equipment used in the collection of Red Blood Cells, Plasma or Platelets."* Clarification is requested regarding the reporting categories assigned to these two changes. From a risk-based perspective, the reporting categories for these two changes appear to be reversed. A change in manufacturer or model, in a manufacturing setting where use of an automated device is standard operating procedure, poses less risk than initial use of the device when considerable process change is required.
21	**B. CBE30** p. 15 3.	Under Contractor Changes, the following sentence was removed with this draft, *"The storage facility may also distribute licensed product to the final user."* It is not clear if this omission is significant in that a registered off-site storage facility may not ship licensed product to the final user, or if the off-site storage facility ships licensed product, that it must be reported in a different category. If appropriate, clarification is requested.
22	**C. 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 (CBE)**	With respect to implementation of a written or audio/visual presentation of a self-administered donor history questionnaire, the draft guidance refers to the July 2003 guidance entitled, "Guidance for Industry: Streamlining the Donor Interview Process: Recommendations for Self-Administered Questionnaires." As already discussed, the November 2010 guidance entitled, "Guidance for Industry: Recommendations for Blood Establishments: Training of Back-Up Personnel, Assessment of Blood Donor Suitability and Reporting Certain Changes to an Approved Application," also provides guidance related to the implementation of a written or audio/visual presentation of a self-administered donor history questionnaire. Although the information in the November 2010 guidance document has been included in this draft, it might be helpful from a historical perspective to include the November 2010 guidance document in the references in this section and to Section IX, References.

Section IV. Recommendations		
Number	**Reference**	**Comment**
	p. 16 1.	
23	**D. Changes to be Described in an Annual Report (Minor Changes) (AR)** p. 17	The second sentence of the second paragraph states, "*You may request an alternative date for the purpose of combining ARs for multiple approved applications into a single AR submission…"* This statement implies that a manufacturer with more than one Biologics License Application may submit a single annual report including all BLAs. For example, that a Source Plasma manufacturer with more than one BLA submit a single Annual Report that reports the changes in each BLA. If this is not correct, this statement should be clarified.
24	**D. AR** p. 17	The third paragraph provides guidance on submitting one original and two copies of an Annual Report for FDA review. The guidance focuses on a paper submission. It is recommended that this section be expanded to include guidance on the use of eSubmitter for submitting Annual Reports. The guidance in general should include a definition for eSubmitter and should provide guidance for submitting all categories. (See also Comments 36 and 39.)
25	**D. AR** p. 17 1.a	Under Product Manufacturing / Procedural Changes, the current (2001) effective guidance document lists, *"Revision of SOP for the following categories if the change is more restrictive <u>than previously approved or is not described</u> in published FDA guidance documents…"* The revised guidance document lists, *"Revision of an SOP for the following categories if the change is more restrictive <u>than previously recommended or described</u> in published FDA guidance documents…"* The word "approved", in the current effective guidance has been interpreted to refer to previously approved Standard Operating Procedures (SOPs). The new language appears to refer only to guidance documents, excluding SOPs. This is a potentially very significant change and clarification is requested.
26	**D. AR** p. 18 1.d	Item 1.d. states, *"Changes in the quality control method if the method is consistent with the manufacturer's directions."* Clarification regarding the word "method" is needed. Does it apply only to testing methods, or does it include other quality control activities such as calibration?
27	**D. AR** p. 18 1.e	The second sentence of item 1.e states, *"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."* It is recommended that this sentence be removed, as it is instructional and more properly belongs in, "Guidance for Industry: Informed Consent

Section IV. Recommendations		
Number	**Reference**	**Comment**
		Recommendations for Source Plasma Donors Participating in Plasmapheresis and Immunization Programs."
28	**D. AR** p. 18 1.g	Item 1.g is, *"Implementation of an approved anti-HIV 1/2 test that includes detection of antibodies to HIV-1 Group O (Ref.15)."* It is recommended that this item be removed, as this change is covered in the August 2009 guidance document, "Guidance for Industry Recommendations for Management of Donors at Increased Risk for Human Immunodeficiency Virus Type 1 (HIV-1) Group O Infection."
29	**D. AR** p. 19 1.m	Item 1.m states, *"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."* As already mentioned, this current thinking is welcome; however, this statement might better be included in a guidance document on donor eligibility, rather than in this document.
30	**D. AR** pp. 19 - 20 2.c and 2.d.	Under Equipment Changes, item 2.c addresses, *"Implementation of software for the donor history questions where staff administers the questions verbally and documents the donor's responses electronically."* Item 2.d.iv addresses, *"Implementation of software that allows establishment personnel to administer the DHQ to the donor and to document donor eligibility."* These two items appear to be the same. If there is an intended difference, it is recommended that the difference be clarified in (as already recommended) an Appendix that lists these types of changes.
31	**D. AR** p. 19 2.d.ii	Under Equipment Changes, item 2.d.ii states, *"Initial installation of commercially available or in-house developed BECS or installation of software upgrades…"* "[C]ommercially available or in-house developed BECS" should be removed and "510(k) cleared BECS or of in-house developed BECS not in interstate commerce" should be inserted so that the sentence states, *"Initial installation of 510(k) cleared BECS or of in-house developed BECS not in interstate commerce or installation of software upgrades…"* This will clarify that the BECS (if not developed in-house, or if in interstate commerce) must be a 510(k) cleared medical device. This change will also address BECS that are developed in-house, but that are in interstate commerce (e.g., in a manufacturer's donor centers across state lines) and therefore must be 510(k) cleared. In addition, and as already mentioned, the terms "initial installation" and "implementation" (2.b.i.) should be standardized or clarified.

Section IV. Recommendations		
Number	**Reference**	**Comment**
32	**D.AR** **p. 20** **2.m**	Under Equipment Changes, item 2.m states, "*Change in manufacturer of automated plasma-only apheresis equipment.*" The 2001 guidance previously stated, "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." We want to confirm changes or upgrades by the device manufacturer are still to be reported as an AR (e.g., Fenwal Auto-C to Aurora).
33	**D. AR** p. 21 3.b	Under Contractor Changes, item 3.b states, *"Temporary use of a previously approved alternate or back-up contractor to perform a manufacturing step."* It is recommended that this item be clarified to indicate whether or not contract testing laboratories are included. Contract testing laboratories are addressed in the note in 3.a, but 3.a does not distinguish between new and previously approved contract testing laboratories that perform infectious disease or ABO/Rh testing. It would also be helpful to clarify the appropriate reporting category for a change in testing laboratory when the change is to a laboratory that is registered to the business entity under one of its BLAs.
34	**D. AR** p. 21 3.b	Under Contractor Changes, the last sentence of 3.b states, *"See sections IV.B. and C. of this guidance."* Correction is needed. The sentence should be, "See sections IV.A. and C. of this guidance."
35	**D. AR** p. 21 3.f	Under Contractor Changes, item 3.f states, *"You should also report the change in address of any unlicensed contractor."* It is recommended that examples be added to (as already mentioned) the Appendix that will contain the list of these types of changes to clarify what is meant by "any unlicensed contractor."
36	**D. AR** p. 21 4.a	Under Facility Changes, item 4.a does not include the statement that, in addition to the AR, manufacturers must submit a facility registration form when reopening a facility after temporary closure, if applicable. A statement similar to that found in item 4.c. should be added to item 4.a.: *"In addition to the AR, you must send in a facility registration form (Form FDA 2830) within 5 days of an opening, move or closure of the site if applicable…"*
37	**D. AR** p. 23 6	The Reporting Format for the AR section of the draft guidance does not address eSubmitter. As already mentioned, it is recommended that this section be expanded

Section IV. Recommendations		
Number	**Reference**	**Comment**
		to include guidance on the use of eSubmitter for submitting Annual Reports. (See also: Comments 24 and 39.)

Section V. Comparability Protocol		
Number	**Reference**	**Comment**
38	**B. Applicability of a Comparability Protocol** p. 25 3.b	Item 3.b. states that a "change with the potential to adversely affect the product" is not appropriate for a Comparability Protocol (CP). It is recommended that the section of this guidance document dealing with Comparability Protocols be revised to describe the intent of this sentence, since any change has the potential to adversely affect the product. Perhaps the use of a Comparability Protocol could be included in the requested algorithm for evaluating a change to determine the appropriate reporting category. An example of an approval as a comparability protocol would be helpful to industry.

Section VI. Labeling Changes Under 21 CFR 601.12(f)		
Number	**Reference**	**Comment**
39	**Labeling Changes Under 21 CFR 601.12(f):** p. 27	The introductory information on page 27 includes: *"A completed Form FDA 2567 'Transmittal of Labels and Circulars Form' should accompany each submission."* PPTA understands that CBER staff have indicated that Form FDA 2567 is no longer required to be included in label submissions. Clarification regarding this point is requested.

Section VII. Submission of Changes to FDA		
Number	**Reference**	**Comment**
40	**Submission of Changes to FDA** p. 29	This section only describes the submission of paper copies of supplements. This section should be expanded to include the use of eSubmitter. In addition, the August 2011 guidance, "Guidance for Industry: Availability of FDA's eSubmitter Program for Regulatory Submissions from Licensed Blood Establishments," should be included in the references.

Section X. Appendix A: Types of Establishments / Facilities and Manufacturing Steps Performed		
Number	**Reference**	**Comment**
41	**Appendix A** p. 32	Appendix A: Types of Establishments / Facilities and Manufacturing Steps Performed It is recommended that a statement describing the purpose and use of this table be included in the guidance document to explain whether the table is meant to address the full range of manufacturing steps

Section X. Appendix A: Types of Establishments / Facilities and Manufacturing Steps Performed		
Number	**Reference**	**Comment**
		performed in the listed facilities or only the core functions.
42	**Appendix A** Plasmapheresis Center Column p. 32	Under Plasmapheresis, the Manual Whole Blood Collection, Whole Blood Component Preparation, and Freeze/Deglycerolize rows are not marked to indicate that some plasmapheresis centers collect Whole Blood for immunization. If the purpose of this table is to identify the range of manufacturing steps that are performed in a facility, then an X should be added to the Manual Whole Blood Collection, Whole Blood Component Preparation, and Freeze/Deglycerolize rows for plasmapheresis centers. (See also: Comment 40.)

Section XI. Appendix B: Reporting Closures, Opening Additional Facilities, Legal Name Changes, Mergers, and Acquisitions		
Number	**Reference**	**Comment**
43	**Appendix B** Legal Name Changes p. 33	The major change row in the table is clearly identified with the words, "Major Change". The minor change row is not identified; only an example is provided. For clarification and consistency, the words, "Minor Change", should be added prior to the word "Example" in the minor change row.
44	**Appendix B** Acquisitions p. 33	On p. 3 of the draft guidance, in the Definitions section, the definition of Acquisition includes, *"…combining facilities operating under different licenses owned by the same corporation so that there is only one surviving license."* This type of acquisition is not included in Appendix B. This type of acquisition should be added to the Acquisitions section of Appendix B.
45	**Appendix B** Product Correspondence p. 33	Appendix B addresses Product Correspondence, but there is no corresponding section in the body of the draft guidance document. As previously mentioned, a section on Product Correspondence should be added to the body of the guidance document. The section should include a description of how eSubmitter is used for product correspondence. In addition, *"U.S. license holder expands its operations to include the opening of a Source Plasma collection center"* is marked as both Product Correspondence and PAS. Correction or clarification is needed.

Section XII. Appendix C: Handling Changes in Facility Relocations		
Number	**Reference**	**Comment**
46	**Appendix C** p. 34	Appendix C is a new addition to the guidance that has the potential to be helpful to industry. It organizes the information by topic, which

		facilitates comparison of the changes by end users. (See also: Document Organization and Format.) However, the listed changes are not as complete, mutually exclusive, or as clearly defined as needed. In addition, historically, "core personnel" has been the concern when evaluating the impact of proposed staffing changes, but "new staff" is introduced for the first time in the entry, *"Relocation of a facility which in turn requires the firm to temporarily close so that new staff can be hired and trained."* In this case, it is not clear whether "new staff" includes staff members who are not core personnel.
47	**Appendix C** p. 34	The first row refers to major changes in Core Personnel. Major changes in Core Personnel should be described. Please clarify "Core Personnel."
48	**Appendix C** p. 34	The fifth row in the table of Appendix C refers to, *"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 equipment."* The equipment type is unclear. "Equipment" should be defined, or examples of changes with respect to equipment be provided. For example, if a facility is approved to use automated blood cell separator devices from two different manufacturers, is the change from one approved manufacturer to the other manufacturer at the time of relocation considered a change in equipment and/or SOPs that would require a PAS?

5) <u>Table of Contents</u>

A suggested Table of Contents for the guidance document that includes the changes recommended above is below. New topics are shown in **bold** font.

I. Introduction
II. Background
III Definitions
IV. Reporting Categories
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) (PAS)
~~1. Product Manufacturing/Procedural Changes~~
~~2. Equipment Changes~~
~~3. Contractor Changes~~
~~4. Facility Changes~~
Algorithm for risk assessment to determine the potential of the change to have a substantial adverse impact on safety and effectiveness of the product (with perhaps an example of application of the algorithm to a change that has a substantial potential to …)

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) (CBE30)

~~1. Product Manufacturing/Procedural Changes~~
~~2. Equipment Changes~~
~~3. Contractor Changes~~
~~4. Facility Changes (see Appendix B of this guidance)~~
Algorithm for risk assessment to determine the potential of the change to have a moderate adverse impact on safety and effectiveness of the product (with perhaps an example of application of the algorithm to a change that has a moderate potential to …)

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 (CBE)

~~1. Product Manufacturing/Procedural Changes~~
~~2. Contractor Changes~~
Algorithm for risk assessment to determine the potential of the change to have a moderate adverse impact on safety and effectiveness of the product (with perhaps an example of application of the algorithm to a change that has a moderate potential to …)

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

~~1. Product Manufacturing/Procedural Changes~~
~~2. Equipment Changes~~
~~3. Contractor Changes~~
~~4. Facility Changes~~
1. Algorithm for risk assessment to determine the potential of the change to have a minimal adverse impact on safety and effectiveness of the product (with perhaps an example of application of the algorithm to a change that has a minimal potential to …)
2. Information that should not be included in the AR
3. Reporting Format for the AR **(including eSubmitter)**

E. Changes to be Described in Product Correspondence

F. Use of 21 CFR 640.120

V. COMPARABILITY PROTOCOL UNDER 21 CFR 601.12(e)

A. Description of a Comparability Protocol
B. Applicability of a Comparability Protocol
C. Content of a Comparability Protocol Submission
D. Submission of a Comparability Protocol and Reporting of the Manufacturing Change(s) Implemented Using an Approved Comparability Protocol
E. Failure to Meet the Criteria of an Approved Comparability Protocol
F. Additional Considerations of a Comparability Protocol

VI. LABELING CHANGES UNDER 21 CFR 601.12(f)
- A. Labeling Changes Requiring FDA Approval Prior to Product Distribution (PAS) (21 CFR 601.12(f)(1))
- B. Labeling Changes Requiring FDA Approval but Product May Be Distributed Prior to FDA Approval (Special Labeling Supplement – Changes Being Effected) (21 CFR 601.12(f)(2))
- C. Labeling Changes Requiring Submission in an Annual Report (21 CFR 601.12(f)(3))

VII. Submission of Changes to FDA
- **A. Supplements**
  - **a. Paper Submissions**
  - **b. eSubmitter**
- **B. Annual Report**
  - **a. Paper Submissions**
  - **b. eSubmitter**

VIII. Failure to Comply Under 21 CFR 601.12(G)
IX. References
X. Appendix A: Types of Establishments/Facilities and Manufacturing Steps Performed
XI. Appendix B: Reporting Closures, Opening Additional Facilities, Legal Name Changes, Mergers, and Acquisitions
XII. Appendix C: Handling Changes In Facility Relocations*
XIII. Appendix D: Reporting changes in BECS
XIV. Appendix E: Reporting Changes in Apheresis Operations and Automated Blood Cell Separator Devices
XV. Appendix F: Reporting Changes in Immunization Programs for Source Plasma Donors
XVI. Appendix G: Reporting Changes in the Manufacture of Leukocytes Reduced Blood Components
XVII. Appendix H: Reporting Changes in Donor and Testing Labs
etc.

Conclusion

PPTA appreciates the opportunity to comment on the Draft Guidance and looks forward to continued work with FDA on revising the recommendations in the 2001 Guidance for certain changes to an approved application based on the experience gained over the last decade. PPTA welcomes from FDA any questions regarding these comments.

Thank you for your consideration.

Respectfully Submitted,

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