Plasma Protein Therapeutics Association

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Division of Inspections and Surveillance (HFM-650)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
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SUBJECT: Compliance Program Guidance Manual
Inspection of Source Plasma Establishments, Brokers,
Testing Laboratories, and Contractors – 7342.002
Implementation Date: April 1, 2011

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (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. The therapies are used in the treatment of a number of rare diseases. The diseases are often genetic, chronic, life-threatening conditions that require patients to receive regular infusions or injections of the therapies for the duration of their lives. Plasma protein therapies include clotting-factor 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.

Introduction

PPTA is pleased to provide these comments on the April 1, 2011, version of the Compliance Program Guidance Manual for the Inspection of Source Plasma Establishments, Brokers, Testing Laboratories, and Contractors – 7342.002 [hereinafter, "Manual"]. The Association strongly supports the Food and Drug Administration (FDA) in its efforts to update the Manual in accordance with its Good guidance practices. However, PPTA suggests additional revisions to the Manual that reflect current industry practice and that recognize the need for regulations as a basis for guidance.

Cross Donation

The Manual recommends, during the inspection, to:

> 13. Review the Source Plasma establishment's procedure to prevent cross donation.
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> Cross donation occurs when (a) an individual donates at more than one Source Plasma establishment or blood collection facility in a geographic area concurrently, (b) donates at one establishment although permanently or temporarily deferred at another, or (3) [sic] donates at a frequency that would be injurious to the donor's health (no more than twice in a 7 day period with two days between donations (21 CFR 640.65(b) and CPG 256.100)).
>
> Review sufficient records to determine if the Source Plasma establishment's written procedures are adequate to identify donors and to prevent cross donation.[1]

PPTA notes that the only factor in Recommendation 13 that references a regulation is the last one; (a) is only a problem if the donor donates more frequently than is allowed, and (b) currently lacks regulatory authority. Although the proposed rule, Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use (2007), extends donor deferral registries to facilities operating under a single license or common management, the rule is not yet final. Thus, establishments are not required to have SOPs that address all three factors in Recommendation 13.

Further, the following recommendation related to 21 CFR 640.65(b) compliance appears elsewhere in the Manual: "During the inspection, a. Review donor record files to determine if the interval between donations is consistent with regulations (21 CFR 640.65)."[2] The following recommendation related to FDA's review of SOPs also appears elsewhere in the Manual: "During the inspection, 1. Review the SOPs for automated collection of Source Plasma. Determine if the Source Plasma establishment collects Source Plasma according to its written procedures approved as part of the license application, and the collection device manufacturer's instructions."[3] As such, the Manual's instruction in Recommendation 13 to "[r]eview sufficient records to determine if the Source Plasma establishment's written procedures are adequate to identify donors and to prevent cross donation" is repetitive and overly broad. For this reason, and because Recommendation 13's definition of "cross donation" is supported only partially by regulation, the recommendation should be deleted from the Manual.

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[1] Manual, p. 38
[2] Manual, p. 47
[3] Manual, p. 46

However, PPTA makes voluntary efforts to protect donors' health. The International Quality Plasma Program (IQPP) was developed in the early 1990s and demonstrated the commitment of PPTA's Source members to collect high-quality, safe starting material (Source Plasma) to produce plasma-derived therapies; the process of updating and optimization of these standards has been ongoing and continues today. To ensure state-of-the-art quality and safety of Source Plasma, companies commit to adhering to all of the IQPP standards, including the Cross Donation Management Standard (CDMS). CDMS acknowledges the necessity of taking measures to protect the health of the donor and to minimize the very rare risk that the donor may attempt to donate more often than is permitted. The measures include centers' completion of donor information forms for use by nearby centers.

Statutory Current Good Manufacturing Practices (CGMP)

PPTA appreciates FDA's recognition in the Manual (unlike previous versions) that

> Source Plasma, Source Leukocytes, and [Therapeutic Exchange Plasma] are not finished pharmaceuticals or finished devices. Therefore, the requirements in the Current Good Manufacturing Practices for Finished Pharmaceuticals regulations at 21 CFR Parts 210 and 211, and the Quality System Regulation at 21 CFR 820 do not apply to these products.[4]

Instead, "manufacturers of Source Plasma, Source Leukocytes, and TEP must comply with the applicable statutory CGMP requirements, the Current Good Manufacturing Practice for Blood and Blood Components requirements in 21 CFR 606 and other applicable regulations in 21 CFR Parts 600-680."[5] Even though "FDA has long recognized that the CGMP requirements in the good manufacturing regulations for finished pharmaceuticals (21 CFR Parts 210 and 211) are valid and applicable ***in concept*** to products for further manufacture into drug products,"[6] the regulations cannot support the detailed recommendations found in the Manual, as reflected in FDA's deletion of all citations to the regulations in the Manual. In previous versions of the Manual, FDA cited the regulations in support of the following recommendations:

- Regulatory/Administrative Strategy
    - Deficiencies: The following, although not all inclusive, are examples of deficiencies that may be indicative of the firm's state-of-control:
        - Quality Assurance System
        - Failure to establish and implement a written quality assurance program

[4] Manual, p. 4
[5] Manual, pp. 4-5
[6] Manual, p. 5

- Lack of computer and/or software validation or a lack of documentation associated with the performance or analysis of validation activities

- Failure to establish and implement adequate computer security provisions (passwords, user authentication, and remote access) to ensure data integrity

- Duplicate, discrepant, or invalid records existing in the computer's donor deferral files that could lead to the acceptance of unsuitable donors and release of unsuitable products

- Failure to establish procedures and/or repeated failure to follow SOPs and/or to maintain appropriate records for the proper handling of post donation information reports

- Quality Assurance System

    - Introductory paragraph

    - Equipment: The Source Plasma establishment's QA procedures should ensure computer systems used in manufacturing comply with regulations

- Computers: During the inspection, user validation of Source Plasma establishment software is required by regulation

In the 2011 Manual, FDA deleted most of the above recommendations; for most of the other recommendations, FDA retained the recommendation but deleted the citation to 21 CFR Part 210 or 211. For one recommendation, FDA rewrote the recommendation, deleted the citation, and noted that 21 CFR Parts 210 and 211 do not apply. In the latter case, FDA expanded the introductory paragraph of Attachment A, Quality Assurance System, of old versions of the Manual (cited to 21 CFR 211.22) to create Attachment B, Quality Assurance System, of the 2011 Manual. Attachment B covers Quality Management Principles, Responsibilities of the Quality Control Unit(s), and Product Quality Review. While FDA also notes that manufacturers must comply with applicable statutory CGMP requirements, 21 CFR 606, and 21 CFR Parts 600-680, citations to supporting regulations in Attachment B are sparse; in fact, none appear under Quality Management Principles, Product Quality Review, or the "During the inspection" section.

Even with the existence of statutory CGMP, FDA lacks the authority to create such detailed, unsupported recommendations. Though manufacturers must comply with applicable statutory CGMP requirements generally, they are not expected to meet the level of detail found in the recommendations without the support of corresponding implementing regulations. As such, PPTA suggests that FDA delete Attachment B or

rewrite it solely with recommendations supported by regulations in 21 CFR Parts 600-680.

Conclusion

PPTA appreciates the opportunity to comment on the Manual and looks forward to continued work with FDA on its efforts to update its Compliance Program Guidance Manuals. The Association welcomes from FDA any questions regarding these comments and/or requests for additional information. Thank you for your consideration.

Respectfully Submitted,

Mary Gustafson
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Plasma Protein Therapeutics Association