Plasma Protein Therapeutics Association

April 29, 2015
Reference No.: FDAA15005 **VIA WEB**

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

SUBJECT: Current Good Manufacturing Practice Requirements for Combination Products; Draft Guidance for Industry and Food and Drug Administration Staff
[Docket No. FDA—2015—D—0198]

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for the opportunity to participate in the guidance development process and is pleased to provide these comments on the draft guidance entitled "Current Good Manufacturing Practice Requirements for Combination Products."[1] PPTA understands that the draft guidance "describes and explains the final rule on current good manufacturing practice (CGMP) requirements for combination products, including presenting general considerations for CGMP compliance as well as analysis of hypothetical scenarios."[2]

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 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.

[1] *See* FR Notice, 80 Fed. Reg. 4280 (January 27, 2015)
[2] *See id.*

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Comments

Section II.B.
Page 7

Section II.B. should reflect the language in the preamble to the final rule that "the rule should [not] be either 'product-based' or 'facility-based.' A manufacturer must comply with the requirements applicable to the activities undertaken at its facility, including applicable aspects of requirements that apply to multiple facilities or the overall manufacturing process for the product, and a product applicant must ensure compliance with all CGMP requirements for its product." In other words, compliance is process-based. As such, PPTA suggests that the section be revised as follows:

As described above, facilities subject to section 4.4(d) may opt to implement a streamlined approach under 21 CFR 4.4(b) by either adopting a drug CGMP-based or QS regulation-based streamlining approach and clearly identifying the approach in their CGMP operating system. While the preamble to the final rule indicates that the rule should not be either "product-based" or "facility-based," the manufacturer may prefer one approach over the other based, for example, on the details of the manufacturing process used at the facility or in light of other manufacturing activities undertaken at the facility.[3]

Section III.C.4.
Page 11

PPTA's reading of Section III.C.4. is that FDA simply is reiterating the definition of "convenience kit" in the preamble to the final rule. As such, PPTA suggests that FDA provide a block quote from the preamble as follows:

4. Convenience kits

As explained in the preamble to the final rule, a

> *kit that includes two or more types of medical products (e.g., a device and a drug), is a combination product and subject to this rule. Accordingly, the manufacture of the products in the kit would also be subject to this rule.*
>
> *An important question, however, in responding to this comment is how to define the term ''convenience kit.'' For purposes of this rule, we define the term to include only kits that solely include products that are: (1) Also legally marketed independently and (2) included in the kit as already packaged for independent marketing and with the same labeling as for*

[3] *See* 78 Fed. Reg. 4313, Comment 14

independent marketing. This is an important question because no additional CGMP requirements generally would apply to the products in such a ''convenience kit'' simply because they have been included in the kit. The only additional CGMP requirements that would generally apply to such a convenience kit would be those applicable to the assembly, packaging, labeling, any sterilization, or further processing of the kit itself. In contrast, if any products to be included in a kit are repackaged, relabeled or otherwise modified for purposes of their inclusion in the kit, the kit is not a ''convenience kit'' for purposes of this rule and all the CGMP requirements applicable under this rule based on any changes made to the constituent parts would apply.[4]

Section III.D.
Pages 12-14

Many of the scenarios about applicability in Section III.D. could be better understood by the reader if summarized in a table or matrix format, allowing the differences in requirements in various scenarios to be easily visualized. For instance, PPTA understands that a "co-packaged" combination product may or may not be a "convenience kit." To provide clarity on requirements for "co-packaged" combination products (not "convenience kits") and "convenience kits," as well as "single entity" combination products, PPTA suggests that FDA add a table as an appendix to the guidance document that could replace or augment Section III.D. PPTA has developed an example table of requirements, which gives guidance depending on the process segment performed by a manufacturing site (CGMP-based or quality system (QS) regulation streamlined approach) and the type of combination product being manufactured (single entity, co-packaged, or convenience kit) (attached). While the example table reflects one interpretation of Section III.D., development of a table by FDA would help avoid divergent interpretations of the section across industry and Agency staff.

Sections IV.A. & IV.B.
Pages 15-27

PPTA appreciates FDA's efforts to help manufacturers understand the purpose and basic content of QS regulation provisions specified in 21 CFR 4.4(b) but is concerned that Sections IV.A. & IV.B. do not provide comprehensive analyses. If comprehensive analyses are not possible, then PPTA suggests that these sections may be more valuable if they simply direct the reader to the applicable regulations, then only include guidance related to combination products, such as verifying requirements are met during combined use.

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[4] *See* 78 Fed. Reg. 4310, Comment 5

Section V.
Pages 30-42

PPTA also appreciates that FDA has provided hypothetical scenarios to focus on specific CGMP considerations relating to CGMP provisions specified in 21 CFR 4.4(b). PPTA notes, however, that all three scenarios are "single entity" combination products, although many of the concerns in the preamble to the final rule were with respect to "co-packaged" combination products, particularly "convenience kits," and in fact, the vast majority of products in the plasma protein therapeutics industry are "co-packaged" combination products. As such, PPTA suggests that FDA add an example of a biologics manufacturer implementing the CGMP streamlining approach to comply with the final rule for co-packing of delivery devices with their products.

Conclusion

PPTA appreciates the opportunity to comment on the draft guidance and looks forward to continued work with FDA on addressing compliance considerations for the final rule on CGMP requirements for combination products. PPTA welcomes from FDA any questions regarding these comments.

Thank you for your consideration.

Respectfully Submitted,

Mary Gustafson
Vice President, Global Regulatory Policy
Plasma Protein Therapeutics Association

Attachment

Example Table

Requirements by Manufacturing Activity and Combination Product Type

Design

(Including design and process changes)

	Single Entity (Pre-filled syringe)	Co-Packaged (Vial with separate novel delivery device, licensed together)	Convenience Kit (Licensed third part syringe included in kit)
cGMP-based Streamline Approach	cGMPs (211/600-680/1271) and: 21 CFR 820.20. Management responsibility 21 CFR 820.30. Design controls 21 CFR 820.100. Corrective and preventive action	Same as single entity, but only aspects relating to combined use	Not applicable, as constituent parts are not designed / developed together
QS Regulation Streamlined Approach	QS Regulation (21 CFR Part 820) and: 21 CFR 211.132. Tamper-evident packaging 21 CFR 211.137. Expiration dating 21 CFR 211.166. Stability testing	Not applicable, constituent parts meet applicable regulations	Not applicable, as constituent parts are not designed / developed together

Manufacturing

Excluding design, but including fabricating, assembling, filling, processing, testing, labeling, packaging, repackaging, holding, and storage)

	Single Entity	Co-Packaged	Convenience Kit
cGMP-based Streamline Approach	cGMPs (211/600-680/1271) and: 21 CFR 820.20. Management Responsibility 21 CFR 820.50. Purchasing controls 21 CFR 820.100. Corrective and preventive action	Same as single entity	Same as single entity
QS Regulation Streamlined Approach	QS Regulation (21 CFR Part 820) and: 21 CFR 211.84. Testing and approval or rejection of components, drug product containers, and closures 21 CFR 211.103. Calculation of yield 21 CFR 211.137. Expiration dating 21 CFR 211.165. Testing and release for distribution 21 CFR 211.167. Special testing requirements 21 CFR 211.170. Reserve samples	Not applicable, constituent parts meet applicable regulations	Not applicable, constituent parts meet applicable regulations

Installation and Servicing (if applicable)

	Single Entity	Co-Packaged	Convenience Kit
cGMP-based Streamline Approach	cGMPs (211/600-680/1271) and: 21 CFR 820.170. Installation 21 CFR 820.200. Servicing	Same as single entity	Same as single entity
QS Regulation Streamlined Approach	QS Regulation (21 CFR Part 820)	Not applicable, constituent parts meet applicable regulations	Not applicable, constituent parts meet applicable regulations