Plasma Protein Therapeutics Association

Date: March 22, 2018
Reference No.: FDAA18004

Submitted Electronically
Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

SUBJECT: Docket No. FDA–1995–D–0288 (formerly Docket No. 95D–0052) for ‘‘Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products; Draft Guidance for Industry”

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) appreciates the opportunity to provide comments on the draft guidance intended to assist applicants and manufacturers of certain licensed biological products in determining which reporting category is appropriate for a change in chemistry, manufacturing, and controls (CMC) information to an approved biologics license application (BLA) as specified in 21 CFR 601.12 (i.e., post-approval changes) (Refs. 1 and 2).

PPTA is the international trade association and standards-setting organization for the world’s major producers of plasma-derived and recombinant analog therapies, collectively referred to as plasma protein therapies. PPTA members are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

Plasma protein therapies are used mostly in the treatment of several 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. These therapies include blood clotting factors for individuals with bleeding disorders, immunoglobulins (IG) to treat a complex of diseases in persons with severe autoimmune deficiencies, therapies for individuals who have alpha-1 anti-trypsin deficiency, which typically manifests as adult-onset emphysema and substantially limits life expectancy, and albumin, which is used to treat individuals with severe liver diseases and, in emergency-room settings, shock, trauma, burns, and other conditions.

PPTA would like to provide comments on the following sections of the draft guidance.

Page Number	8, Section C
Current Text	Text about impacted CTD sections should be added as proposed to this section which describes the type of information that should be provided.

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Proposed Change	Updated CTD section(s) impacted by the change, should be life cycled accordingly into the BLA.
Rationale	In accordance with the ICH M2 Expert Working Group eCTD specification guidelines, "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use – Life Cycle Management", CTD sections should be life cycled to reflect current information.

Page Number	8, Section C
Current Text	Relevant validation protocols and data; and
Proposed Change	Delete "protocols" and replace with "reports or summaries of reports"
Rationale	The validation reports provide detail of the protocol and any deviations as well as the data, it is not necessary to provide the protocols as well

Page Number	8, Section C
Current Text	A cross-reference to relevant validation protocols and/or SOPs
Proposed Change	Delete "protocols" and replace with "reports or summaries of reports"
Rationale	The validation reports provide detail of the protocol and any deviations as well as the data, it is not necessary to provide the protocols as well.

Page Number	9, Section D
Current Text	A CP, or a change to a CP, shall be submitted as a PAS (a major change) requiring approval from the FDA before distribution of a product made using the change outlined in the protocol. If approved, the CP may justify a less burdensome reporting category for the particular change.
Proposed Change	Delete: "If approved, the CP may justify a less burdensome reporting category for the particular change." Insert: "If approved, the CP serves as a commitment by the applicant to perform the specified activities outlined in the CP that can justify a reduced reporting category. Notification of the change(s) should be

	submitted using the reporting category specified in the approved CP submission if all of the predefined criteria for success in the approved CP have been met."
Rationale	The current text in the guidance may result in an interpretation of the statement to mean that upon approval of the CP, the applicant could start distributing the product

Page Number	10, 2nd paragraph
Current Text	Some manufacturing changes may be reporting in multiple categories
Proposed Change	After "categories", insert: "or impact multiple products…. When the same or multiple related changes impact multiple products sponsors may choose to submit one dossier and cross-reference all impacted dossiers accordingly."
Rationale	In order to save time and resource for both sponsors and the FDA, allowing the same data package/dossier for one impacted product be leveraged, where appropriate, for all impacted products should be an option.

Page Number	10, Section F
Current Text	Established Conditions are defined by the FDA as the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy, as defined in an application, that assure process performance and quality of an approved product.
Proposed Change	After "quality of an approved product." Insert: "It is recognized that not all legacy filings will have documented Established Conditions. If Established Conditions are not documented in the BLA sponsors should continue to assess changes as described in Section B."
Rationale	Legacy products may not have dossiers which identify Establish Conditions. Further, older products may not have detailed or CTD compliant dossiers. In these instances, sponsors should be always assessing the potential for the change to impact product quality as it

	may relate to the safety or effectiveness of the product, regardless of what information was historically filed.

Page Number	11, Section V.A.
Current Text	Any change to process parameters (operating or performance) outside of an approved validated range(s) should be evaluated with respect to criticality, impact on process performance and product quality, and effectiveness of the overall control strategy and must be reported to FDA.
Proposed Change	After "FDA", insert: Changes within the validated range should be assessed and documented internally but need not be submitted to FDA unless a risk to product is noted by the Company review.
Rationale	Currently it is not clear what happens for changes within validated parameters. Flow charts and information within the eCTD often present the normal operating range (NOR) at which the Company operate the process. However, this is usually tighter than the Proven Acceptable Range (PAR or validated range). Therefore, according to Section V.A. of the proposed guidance Companies should be able to make changes within the validated range i.e. widen or tighten the NOR without notifying FDA.

Conclusion

PPTA appreciates the opportunity to provide comments concerning the draft guidance intended to assist applicants and manufacturers of certain licensed biological products in determining which reporting category is appropriate for a change in chemistry, manufacturing, and controls (CMC) information to an approved biologics license application (BLA). PPTA welcomes any questions or comments regarding our response. Thank you for your consideration.

Respectfully submitted,

Mary Gustafson
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Plasma Protein Therapeutics Association