Plasma Protein Therapeutics Association

Date: November 25, 2015
Reference No.: FDAA15010 VIA EMAIL

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

SUBJECT: Request for Quality Metrics; Notice of Draft Guidance Availability and Public Meeting; Request for Comments [Docket No. FDA–2014–D–2537]

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opportunity to participate in the guidance development process and is pleased to provide these comments on the Agency's draft guidance, entitled "Request for Quality Metrics; Guidance for Industry."[1] As an industry association, PPTA has the opportunity to discuss issues of interest to the Association and FDA at an annual liaison meeting held primarily with representatives from the Center for Biologics Evaluation and Research (CBER). PPTA appreciates CBER's participation at our liaison meeting on September 16, 2015, in Bethesda, Maryland, and the dialogue provided regarding this subject.

PPTA understands that the draft guidance includes an explanation of how FDA intends to use quality metrics data to further develop FDA's risk-based inspection scheduling, to identify situations in which there may be a risk for drug supply disruption, to improve the efficiency and effectiveness of establishment inspections, and to improve FDA's evaluation of drug manufacturing and control operations. FDA expects that the initial use of the metrics will be to consider a decreased surveillance inspection frequency for certain establishments. For example, establishments that have highly controlled manufacturing processes have the potential to be inspected less often (as a lower priority for inspection) than similar establishments that demonstrate uncontrolled processes (as a higher priority for inspection). In addition, FDA intends to consider whether these metrics may provide a basis for FDA to use improved risk-based principles to determine the appropriate reporting category for postapproval manufacturing changes.[2]

About PPTA

PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies,

[1] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm455957.pdf accessed September 21, 2015

[2] *See* FR Notice, 80 Fed. Reg. 44973, 44983 (July 28, 2015)

collectively referred to as plasma protein therapies. Plasma protein therapies 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. These therapies include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a complex of diseases in persons with immune 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 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

PPTA supports the continued development of FDA's risk-based approach as outlined in the draft guidance and views this as a benefit to the entire pharmaceutical industry. The principles outlined in the draft guidance clearly support the goals of "Pharmaceutical cGMPs for the 21st Century" by moving toward "a maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight." However, we feel that stronger transparency in how the metrics provided to the Agency will be collated, reviewed and compared to each other is necessary for the industry to ensure the Agency receives the correct information in the most useful way every time.

As noted in the draft guidance (Page 14, Lines 525-526) and discussed at our liaison meeting, manufacturers, including PPTA member companies, currently maintain quality system performance information and metrics in accordance with 21 CFR 211. Additionally, all quality system expectations established in the CFR extend to human plasma derived therapies. As presented at the liaison meeting, PPTA is concerned by the fact that human plasma derived therapies have been specifically excluded from the draft guidance and requests that FDA change the wording of the relevant draft guidance sections (Page 2, Lines 61-64 and Page 10, Lines 363-367) to remove this exclusion.

PPTA requests that FDA consider removal of this exclusion for the following reasons:

1) This exclusion implies to PPTA, our patient communities and healthcare providers that the quality systems established by member companies are not capable of being, or are not currently, in compliance with existing regulatory expectations. PPTA disagrees with this implication based on the current compliance standing of its' member companies and believes that the concern that this may raise, or has already created, with patients and healthcare providers in relation to how this may reflect on final product quality is not justified.

2) As mentioned previously, PPTA fully supports this initiative and the stated objectives of the draft guidance. In the absence of a removal of the exclusionary language, member companies, while being expected to comply with all

applicable CFR requirements, will essentially be penalized by not being able to benefit from reduction in inspection frequency or changes in regulatory filing categorization. PPTA recognizes that other data are being considered in the overall risk-based approach put forward by FDA; however, as stated in Section II.B. "The quality metrics program is expected to play an important role in addressing risk-based inspection scheduling…." As such, PPTA believes that the exclusion clauses of the draft guidance will have a negative impact on companies in terms of their ability realize reduced inspection frequency or advantage in regulatory filing categorization. Plasma manufacturers will be denied the opportunity to operate in the regulatory environment described as the vision of "Pharmaceutical cGMPs for the 21st Century."

3) FDA asserts in Section III.B. that the request for quality metric information is not different than other information requests made in advance of a site inspection. PPTA fully expects that, despite being excluded from scope of the draft guidance, FDA inspectors will continue to request this information while performing on-site inspections. Concerns with this potential outcome include:

    a. PPTA companies will have to maintain the data, regardless of inclusion in the draft guidance; it simply won't be requested in advance of inspections.

    b. Instead of the quality metrics data being reviewed and considered by a central review team within the Agency, within the context of the full body of quality data and in comparison to other companies in industry, it will be interpreted by the individual inspectors which will result in inherent variation of and subsequent application of the data.

    c. The guidance states that the value of having this information prior to inspections is to "assist staff in preparing for in-person inspections, to improve their efficiency and effectiveness." The implication for PPTA member companies is that, by comparison to firms included in the draft guidance, they will be subject to inspections which are less efficient and, as a result, likely longer in duration. Substantial resources are expended to properly support an on-site FDA inspection and, as the draft guidance is currently written, implies that manufacturers of human plasma derived therapies will incur a higher resource burden during FDA inspections, by comparison to other pharmaceutical manufacturers.

4) The draft guidance will serve to create inefficiencies at establishments that manufacture products that are both included in the scope of the draft guidance and those that are excluded from the draft guidance.

    a. Establishments which manufacture human plasma derived therapies in addition to products which fall within the draft guidance will be required to maintain different reporting systems based on product line inclusion or exclusion.

b. The firms will have only partial consideration given to the overall quality compliance and performance at the manufacturing site. As data for human plasma derived products are excluded from consideration for the quality metrics reporting, the data utilized in FDA's evaluation of the site for reduced inspection frequency will be incomplete and could result in inappropriate decision-making as it relates to overall site performance.

Comments on draft guidance

Page	Section	Language	Comments/ Recommendations
2	I.	The requests would not apply to: establishments that are not required to register under section 510 of the FD&C Act and regulations FDA has issued at 21 CFR 207.10; compounders operating under section 503A or registered as outsourcing facilities under section 503B of the FD&C Act; medical gas manufacturers; positron emission tomography manufacturers; and manufacturers of blood and blood components for transfusion, vaccines, cell therapy products, gene therapy products, allergenic extracts, human cells, tissues, and cellular and tissue based products and non-recombinant versions of plasma derived products.	PPTA requests removal of language which excludes human plasma derived therapeutics from the scope of the guidance.
10	V.A.1	Additionally, the requests would not apply to persons and establishments that are not required to register under section 510 of the Act and regulations FDA has issued at 21 CFR 207.10; compounders operating under section 503A or registered as outsourcing facilities under section 503B of the FD&C Act; medical gas manufacturers, positron emission tomography manufacturers, or manufacturers of blood and blood components for transfusion, vaccines, cell therapy products, gene therapy products, allergenic extracts, human cells, tissues, and cellular and tissue based products and non-recombinant versions of plasma derived products. For purposes of this guidance, we will refer to the establishments whose owners or operators are subject to FDA's requests as "covered establishments."	PPTA requests removal of language which excludes human plasma derived therapeutics from the scope of the guidance.

Conclusion

PPTA appreciates the opportunity to comment on the draft guidance, estimate of burden, and questions to stakeholders and looks forward to continued work with FDA on Quality Metrics. PPTA welcomes from FDA any questions regarding these comments.

Thank you for your consideration.

Respectfully submitted,

Mary Gustafson
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Plasma Protein Therapeutics Association