Plasma Protein Therapeutics Association

September 13, 2013
Reference No.: FDAA13020 **VIA WEB**

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

SUBJECT: Draft Guidance for Industry on Circumstances That Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection
[Docket No. FDA—2013—D—0710]

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for the opportunity to participate in the guidance development process and is pleased to provide these comments on the Draft Guidance for Industry: Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection (July 12, 2013).[1] PPTA understands that section 707 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112—144), signed into law on July 9, 2012, adds section 501(j) to the Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 351(j)) to make a drug adulterated that "has been manufactured, processed, packed, or held in any factory, warehouse, or establishment and the owner, operator, or agent of such factory, warehouse, or establishment delays, denies, or limits an inspection, or refuses to permit entry or inspection."[2] PPTA appreciates that FDA issued the Draft Guidance, as required by FDASIA section 707(b), to define the type of action, inaction, and circumstances that the Agency considers to constitute delaying, denying, or limiting inspection, or refusing to permit entry or inspection for the purposes of FD&C Act section 501(j).[3]

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, 78 Fed. Reg. 42387 (July 15, 2013)
[2] *See id.*
[3] *See id.*

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General Comments

PPTA recognizes that, as noted in the Draft Guidance, FD&C Act section 704(a)(1) authorizes FDA "to enter, *at reasonable times*, any [facility and] to inspect, *at reasonable times* and *within reasonable limits* and *in a reasonable manner*, such [facility]"[4] and agrees with the Agency's characterization that "[c]ourts have upheld the legality of an FDA inspection if it is conducted at a reasonable time, within reasonable limits and in a reasonable manner."[5] PPTA also recognizes that FDASIA section 706 closely mirrors the "reasonable" language of FD&C Act section 704(a)(1) in adding FD&C Act section 704(a)(4), which, as also noted in the Draft Guidance, authorizes FDA to request records "in advance of or in lieu of an inspection, *within a reasonable timeframe*, *within reasonable limits*, and *in a reasonable manner* … ."[6]

PPTA would expect that the statutory "reasonable" phrases – "at reasonable times," "within reasonable limits," "in a reasonable manner," and "within a reasonable timeframe" – also would appear in the Draft Guidance. In fact, while the "in a reasonable manner" phrase does appear in the Draft Guidance (line 97), several other "reasonable" phrases also appear, as follows:

- within a reasonable time (line 77)
- reasonable accommodations (line 78)
- reasonable explanation (lines 83-84, 86, 121, and 165)
- reasonable amount of time (line 119)
- within a specific, reasonable timeframe (line 126)
- reasonable access (line 159)
- redaction … considered reasonable (footnote 5)

"Unreasonable" phrases – "delays … not be considered unreasonable" (lines 99-100), "for an unreasonable period of time" (line 108), and "unreasonable redaction" (footnote 5) – also appear in the Draft Guidance. However, the terms "reasonable" and "unreasonable" are not defined in the Draft Guidance and are subject to variable interpretation. It would be helpful if FDA were to include concrete examples that demonstrate the meaning of "reasonable" and "unreasonable."

In general, PPTA asks that FDA consider the intent of the facility in making its reasonable/unreasonable determination. For example, if after scheduling an inspection, a facility requests a later start date without giving what appears to FDA to be a "reasonable explanation," then a discussion should occur between the Agency and the facility about the explanation. PPTA recognizes that there may, in fact, come a time when the two parties would disagree, and FDA would determine that the explanation was "unreasonable" such that the inspection was delayed; however, an effort should be made to initiate such discussions to avoid misunderstandings and to establish the facility's intent as an important, though not dispositive, part of the Agency's reasonable/unreasonable determination. PPTA's below suggested revisions, while not exhaustive, are illustrative of the Association's general comment.

Lines	Current	Revised
85—86	After scheduling an inspection, a facility requests a later start date without giving a reasonable explanation.	After scheduling an inspection, a facility requests a later start date without giving a reasonable explanation, *after reasonable efforts were made by FDA to discuss the explanation with the facility.*
120—	a delay in producing records to	a delay in producing records to FDA without

[4] *See* 21 U.S.C. 374(a)(1) (emphases added)
[5] *See* Draft Guidance at n.3
[6] *See* 21 U.S.C. 374(a)(4)(A) (emphases added)

122	FDA without reasonable explanation may be considered delaying the inspection.	reasonable explanation, *after reasonable efforts by the Agency to discuss the explanation with the facility*, may be considered delaying the inspection.

Specific Comments

The Draft Guidance indicates that FDA's interpretation of the term "refuses to permit entry or inspection" includes "passive behavior and non-action by the owner, operator, or agent of a drug facility …" (lines 214—215) and gives the following as one of three examples: "Following FDA's attempt to contact the facility's designated contact(s), the facility fails to respond" (lines 219 and 224—225). Non-action as a basis for determining that an owner, operator, or agent of a drug facility has refused to permit entry or inspection has the potential to be misapplied. For example, a facility's designated contact's failure to respond could be caused by FDA's failure to reach the contact. PPTA respectfully requests that FDA qualify its interpretation with the caveat "where there is a reasonable expectation of non-passive behavior or action by the owner, operator, or agent of the drug facility," as reflected in the Association's suggested revisions below.

Lines	Current	Revised
214—216	FDA interprets the term "refuses to permit entry or inspection" to include passive behavior and non-action by the owner, operator, or agent of a drug facility that results in an authorized representative of the FDA not being able to enter or inspect the facility.	FDA interprets the term "refuses to permit entry or inspection" to include passive behavior and non-action by the owner, operator or agent of a drug facility, *where there is a reasonable expectation of non-passive behavior or action by the owner, operator, or agent of the drug facility,* that results in an authorized representative of the FDA not being able to enter or inspect the facility.
224—225	Following FDA's attempt to contact the facility's designated contact(s), the facility fails to respond.	Following FDA's attempt to contact the facility's designated contact(s*), to which there is a reasonable expectation of a response,* the facility fails to respond.

Conclusion

PPTA appreciates the opportunity to comment on the Draft Guidance and looks forward to continued work with FDA on defining the type of action, inaction, and circumstances that the Agency considers to constitute delaying, denying, or limiting inspection, or refusing to permit entry or inspection for the purposes of FD&C Act section 501(j). 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