Plasma Protein Therapeutics Association

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Reference No.: FDAA12010

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

VIA U.S. MAIL

SUBJECT: Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed
[Docket No. FDA-2011-N-0912]

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) is pleased to provide these comments on Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed ("FR Notice").[1] PPTA recognizes that these comments are being submitted after FDA's deadline of March 27, 2012, but hopes that, nonetheless, they will be considered by the Agency during its analysis of this important issue. PPTA understands that FDA's request for information and comments responds to a July 2011 citizen petition, filed on behalf of seven prescription drug manufacturers, seeking additional clarification on areas of FDA policy regarding distribution of prescription drugs.[2] PPTA looks forward to additional opportunities to comment on at least some of the remaining issues raised in the citizen petition.

About PPTA

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, which 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 plasma protein therapies for the duration of their lives. The 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,

[1] *See* FR Notice, Request for Information and Comments, 76 Fed. Reg. 81,508 (Dec. 28, 2011)
[2] *See id*. at 81,508

147 Old Solomons Island Road · Suite 100 · Annapolis, MD 21401 USA
tel: 202.789.3100 · 410.263.8296 · fax: 410.263.2298 · e-mail: ppta@pptaglobal.org · www.pptaglobal.org
PPTA Offices in Washington · Annapolis · Brussels · Tokyo

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 recognizes the need for additional clarification on at least some areas of FDA policy regarding distribution of prescription drugs as described in the citizen petition. As described below, PPTA respectfully requests that FDA take necessary steps to increase the clarity, predictability, and fairness of its "scientific exchange" safe harbor and to maintain its scope, if not make it broader. In separate comments also submitted to FDA today, PPTA also responds to the Agency's separate request for comments on the Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices: Draft Guidance ("Draft Guidance") arising, in part, from the citizen petition ("Draft Guidance Comments").[3] PPTA incorporates the Draft Guidance Comments here by reference.

PPTA supports access to all medically necessary plasma protein therapies

As described in the Draft Guidance Comments, off-label uses of prescription drugs including plasma protein therapies are lawful.[4] PPTA supports the right of the treating physician to determine when the use of a particular therapy is medically necessary, including when such use is off-label. In many cases, such use is a vital component of patient access to medically necessary care.

FDA has recognized value of off-label information through multiple safe harbors

Also described in the Draft Guidance Comments, FDA generally does not allow manufacturer[5] statements promoting off-label uses; according to the Agency, manufacturer statements that promote a drug for a use other than those approved or cleared by the Agency may be used as evidence of a new intended use and, thus, of "misbranding."[6] However, FDA also has recognized that off-label information is valuable; as such, FDA has established multiple safe harbors.[7] In addition to a "scientific exchange" safe harbor, FDA also has established safe harbors for responses to "unsolicited requests," dissemination of reprints, and continuing professional education.[8]

FDA established the "scientific exchange" safe harbor via regulation. 21 C.F.R. § 312.7 prohibits sponsor or investigator representation "in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under

[3] *See* Draft Guidance, Availability, 76 Fed. Reg. 82,303 (Dec. 30, 2011)
[4] *See* Draft Guidance Comments at 2-3
[5] For the remainder of this letter, PPTA uses the terms "firm" and "manufacturer" interchangeably
[6] *See* Draft Guidance Comments at 3-4
[7] *Id.* at 4
[8] *Id.* at 5-6

investigation" or other promotion of the drug.[9] However, "[t]his provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media."[10] FDA most recently delineated the "scientific exchange" safe harbor in the preamble to part of the final Investigational New Drug, Antibiotic, and Biologic Drug Product Regulations ("IND Regulations") by providing requirements and examples of "scientific exchange."[11]

"Scientific exchange" safe harbor should be clear, predictable, and fair

PPTA members desire clarity, predictability, and fairness in FDA's application of its safe harbor. As noted above, the safe harbor most recently is reflected only in a preamble to part of the final IND Regulations. As preambles are not as readily available as the regulations themselves, PPTA asks that FDA take whatever steps are deemed necessary to ensure the Agency's interpretation of its safe harbor is clear, predictable, and fair.

FR Notice questions

- *How should FDA define scientific exchange?*
- *What types of activities fall under scientific exchange?*
- *What types of activities do not fall under scientific exchange?*
- *Are there particular types and quality of data that may indicate that an activity is, or is not, scientific exchange?*
- *What are the distinctions between scientific exchange and promotion? What are the boundaries between scientific exchange and promotion?*[12]

FDA should maintain its "scientific exchange" safe harbor, if not make it broader

As noted above, FDA most recently delineated the "scientific exchange" safe harbor in the preamble to part of the final IND Regulations. Statements are "made in the exchange of scientific information" if they:

> (1) make clear that the drug is investigational;
> (2) make no claims that the drug has been proven to be safe or effective; and
> (3) [are] truthful and nonmisleading when measured against available information on the drug—and fairly represent available

[9] *See* 21 C.F.R. § 312.7
[10] *Id.*
[11] *See* IND Regulations, Treatment Use and Sale, 52 Fed. Reg. 19,466 (May 22, 1987)
[12] FR Notice, 76 Fed. Reg. at 81,509

> information—as set forth in materials such as investigators brochures and patients' informed consent sheets.[13]

The following types of "free exchange of scientific information" are not limited: "publishing results of scientific studies, letters to the editor in defense of public challenges, [and] investigator conferences."[14] As discussed in the Draft Guidance Comments, recent First Amendment case law raises questions regarding FDA's off-label enforcement authority.[15] As such, FDA is compelled, at the least, to maintain its safe harbor policies, if not to expand them.

Further, FDA should issue a draft guidance with examples of the "scientific exchange" safe harbor. PPTA suggests that FDA expand on and add to the above examples of "scientific exchange." Comments to this docket likely will provide FDA with relevant information to draft such a guidance. As technologies change, the guidance can be revised and/or new draft guidances can be issued.

Additional FR Notice questions

At this time, PPTA is unable to provide answers to question in the FR Notice regarding the activities of marketing/communications personnel.[16] As noted above, PPTA encourages FDA to use such answers in the docket to draft a guidance with examples of "scientific exchange." However, PPTA can provide answers to the following additional questions in the FR Notice:

- *How should the Agency treat scientific exchange concerning off-label uses of already approved drugs and new uses of legally marketed devices? Please address whether there should be any distinctions between communications regarding uses under FDA-regulated investigation (to support potential approval) and communications regarding uses that are not under express FDA-regulated investigation.*[17]

As described above, FDA should at least maintain its "scientific exchange" safe harbor regarding off-label uses of investigational drugs, if not broaden it. In light of *Sorrell*, PPTA suggests that FDA broaden the safe harbor to include off-label uses of already approved drugs that are not investigational. In other words, there should be no distinction between communications concerning off-label uses of already approved drugs under FDA-regulated investigation (to support potential approval) and those not under express FDA-regulation investigation; the safe harbor should protect both types of communications.

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[13] IND Regulations, 52 Fed. Reg. at 19,475
[14] *Id.*
[15] *See* Draft Guidance Comments at 6-7 (citing *Sorrell v. IMS Health*, 131 S.Ct. 2653 (2011))
[16] *See* FR Notice, 76 Fed. Reg. at 81,509
[17] *Id*.

- *How should the Agency treat scientific exchange concerning use of products that are not yet legally marketed (that is, products that cannot be legally distributed for any use outside of an FDA- or institutional review board (IRB)-approved clinical trial)?*[18]

At this time, the "scientific exchange" safe harbor should not be expanded to include communications concerning use of products that are not yet legally marketed (unless the use of the product is under FDA-regulated investigation to support potential approval). PPTA understands that *Sorrell* and FDA's current safe harbors do not address such communications but contemplate communications concerning uses of products that are legally marketed and/or under FDA-regulated investigation to support potential approval. Broadening of the safe harbor in the manner previously described, however, is warranted.

Conclusion

PPTA appreciates the opportunity to provide these comments on Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed and looks forward to continued work with FDA on efforts to clarify areas of Agency policy regarding distribution of prescription drugs. PPTA welcomes from FDA any questions regarding these comments or requests for more information.

Thank you for your consideration.

Respectfully Submitted,

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

[18] *Id.*