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

VIA WEB

SUBJECT: Revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices; Availability [Docket No. FDA-2008-D-0053]

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) is pleased to provide these comments on the Revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses (“Revised Draft Guidance”).¹ PPTA understands that the Revised Draft Guidance, in part, responds to the July 2011 and September 2013 citizen petitions, filed on behalf of a number of prescription drug manufacturers, seeking additional clarification on several areas of FDA policy regarding distribution of prescription drugs.² PPTA also understands that the Revised Draft Guidance is one of multiple draft guidances FDA plans to publish that address questions and issues related to the distribution of scientific and medical information reflecting unapproved or uncleared uses.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. 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

¹ Dep’t of Health & Human Servs., Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices; Revised Draft Guidance (“Revised Draft Guidance”) (February 2014), *available at* <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm387652.pdf>.

² 79 Fed. Reg. 11,793, 11,793 (Mar. 3, 2014).

³ *Id.*

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.

General comments

PPTA commends FDA for publishing the Revised Draft Guidance and planning to publish additional draft guidances related to the distribution of scientific and medical information reflecting unapproved or uncleared uses. As described below, PPTA respectfully requests that FDA take necessary steps to increase the clarity, predictability, and fairness of the safe harbors outlined for the distribution of scientific and medical publications to health care professionals or health care entities. PPTA looks forward to additional opportunities to comment on future draft guidances related to this subject matter and on at least some of the remaining issues raised in the citizen petitions.

PPTA supports access to all medically necessary plasma protein therapies

Off-label uses of prescription drugs including plasma protein therapies are lawful

In the Revised Draft Guidance, FDA recognizes “the value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved new uses.”⁴ In fact, “[n]othing in [the Federal Food, Drug, and Cosmetic Act (FDCA)] shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.”⁵ Similarly, 21 C.F.R. part 312 (FDA’s regulations on investigational new drug applications) “does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.”⁶ Further, reimbursement is allowed by payors in federal health care programs for off-label uses that are “medically necessary”;⁷ in fact, when the use is a “medically accepted indication,” reimbursement is mandated.⁸ Such indications include those supported by one or more citations included or approved for inclusion in any of three compendia.⁹

⁴ Revised Draft Guidance at 6.

⁵ 21 U.S.C. § 396.

⁶ See 21 C.F.R. § 312.2(d).

⁷ See 42 U.S.C. § 1396r-8(g)(1)(A)(ii).

⁸ See 42 U.S.C. § 1396r-8(d)(1)(B)(i).

⁹ 42 U.S.C. § 1396r-8(k)(6). The three compendia are the American Hospital Formulary Service Drug Information, the United States Pharmacopeia-Drug Information (or its successor publications), and the DRUGDEX Information System. 42 U.S.C. § 1396r-8(g)(1)(B)(i).

Patients rely on medically necessary, off-label uses of plasma protein therapies

In the Revised Draft Guidance, FDA also recognizes that scientific or medical publications on unapproved new uses can be “particularly important,” given that a health care professional can generally choose to use or prescribe an approved or cleared medical product for an unapproved use, if the off-label use is appropriate based on his or her judgment.”¹⁰ In fact, 21% of all prescription drug use¹¹ and, according to Journal of the American Medical Association physician-writer Tracy Hampton, 90% of prescription drug use for treatment of rare diseases is off-label. As noted, plasma protein therapies manufactured by PPTA members are used in the treatment of a number of rare diseases. Off-label uses of plasma protein therapies are not frivolous but are medically necessary uses as determined by patients’ treating physicians. As such, these uses are vital to patient access.

FDA generally does not allow manufacturer statements promoting off-label uses

FDCA prohibits firms¹² from introducing “new drugs” into interstate commerce for any intended use that FDA has not determined to be safe and effective¹³ and ensures that the manufacturer’s proposed labeling for a “new drug” is not “false or misleading in any particular.”¹⁴ FDCA deems a drug misbranded “unless its labeling bears ... adequate directions for use”¹⁵ but exempts prescription drugs from the “adequate directions” requirement if the label contains “the directions for use and cautionary statements, if any, contained in such prescription.”¹⁶ FDCA also authorizes FDA to promulgate regulations exempting certain drugs from the “adequate directions” requirement where the government finds the requirement “is not necessary for the protection of the public health.”¹⁷ As such, FDA has required for exemption that “[l]abeling on or within the package from which the drug is to be dispensed bears adequate information for its use ... for the purposes for which it is intended”¹⁸ For FDA, “intended use” is informed by “the objective intent of the persons legally responsible for the labeling of drugs”; a manufacturer that “knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes,

¹⁰ Revised Draft Guidance at 6.

¹¹ Liang *et al.*, Reforming Off-Label Promotion to Enhance Orphan Disease Treatment, *Science* 327 (5963): 273-74.

¹² For the remainder of this letter, PPTA uses the terms “firm” and “manufacturer” interchangeably.

¹³ See 21 U.S.C. §§ 331(d), 355(a).

¹⁴ See 21 U.S.C. § 335(d).

¹⁵ See 21 U.S.C. § 352(f)(1).

¹⁶ See 21 U.S.C. § 353(b)(2).

¹⁷ See 21 U.S.C. § 352(f)(1).

¹⁸ See 21 C.F.R. § 201.100(c)(1).

or uses other than the ones for which he offers it [must] provide adequate labeling for such a drug which accords with such other uses”¹⁹

In other words, if FDA determines that a manufacturer “objectively intends” off-label uses of its drug, then the drug is subject to the “adequate directions” requirement and, thus, is “misbranded” under FDCA. FDA has based this determination

not only on information provided “with” the product, but also ... on information disseminated by manufacturers in other contexts, such as scientific and educational meetings and symposia, books, and articles, in part because all of these materials can create new intended uses for the products, which must be reflected in the labeling of the products.²⁰

FDA believes that “[p]romotion of unapproved uses can encourage physicians and patients to make decisions based on statements or claims that are, in many cases, supported by little or no data.”²¹ As such, according to FDA, 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”²² and, thus, of “misbranding.”

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

It is well accepted and non-controversial that off-label use, and the truthful, non-misleading information that supports it, are often vital to patient care. As the American Medical Association has recognized, “[u]p to date, clinically appropriate medical practice at times requires the use of pharmaceuticals for ‘off-label’ indications.”²³ Likewise, FDA has confirmed the value of this information by establishing and updating the safe harbors in question – for scientific or medical journal articles, scientific or medical reference texts, and clinical practice guidelines (“CPGs”) – as well as multiple other safe harbors (e.g. responses to unsolicited requests, scientific exchange, distribution of reprints, and continuing professional education).

¹⁹ See 21 C.F.R. § 201.128.

²⁰ See Citizen Petition Regarding the Food and Drug Administration’s Policy on Promotion of Unapproved Uses of Approved Drugs and Devices, Request for Comments, 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994) (“1994 FR Notice”).

²¹ See *id.*

²² See Dep’t of Health & Human Servs., Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices: Draft Guidance (December 2011), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf> at 2.

²³ Memorandum of the AMA House of Delegates, Resolution 820, Off-Label Use of Pharmaceuticals (Sept. 21, 2005), available at <http://www.ama-assn.org/meetings/public/interim05/820i05.doc>.

Recent First Amendment case law raises questions regarding FDA's off-label enforcement authority

PPTA notes the recent U.S. Supreme Court decision, *Sorrell v. IMS Health*,²⁴ which invalidated Vermont's Prescription Confidentiality Law restricting the sale, disclosure, and use of pharmacy records that reveal the prescribing practices of individual doctors. The law prevented "detailers" employed by pharmaceutical manufacturers from using prescriber-identifying information to market the manufacturers' brand-name drugs but permitted pharmacies to sell the information for purposes such as "health care research" and insurers, researchers, journalists, Vermont itself, and others also to use the information. The court found that the prohibited speech was protected by the free speech clause of the First Amendment and, because the law was designed to impose a specific, content- and speaker-based restriction, heightened judicial scrutiny was warranted. Because Vermont's asserted interest in physician confidentiality could not justify the burden placed on the protected expression, the law was struck down.

FDA's current regulatory framework regarding manufacturer dissemination of off-label information restricts speech in a manner similar to the Vermont law. Thus, *Sorrell* questions the validity of the regulations under which FDA prohibits manufacturer dissemination of off-label information. In fact, Justice Steven Breyer, in *Sorrell's* dissent, warns that "the same First Amendment standards that apply to Vermont here would apply to similar regulatory actions taken by ... the Federal Government acting, for example, through [FDA] regulation."²⁵ Justice Breyer also gives FDA's off-label regulation as an example of a speaker-based restriction, similar to the Vermont law, in sentiments that PPTA echoes:

Such a firm, for example, could not suggest to a potential purchaser (say, a doctor) that he or she might put a pharmaceutical drug to an "off label" use, even if the manufacturer, in good faith and considerable evidence, believes the drug will help. All the while, a third party (say, a researcher) is free to tell the doctor not to use the drug for that purpose.²⁶

More recently, the U.S. Court of Appeals for the Second Circuit issued a decision, *United States v. Caronia*,²⁷ that used the *Sorrell* Court's two-step analysis to determine whether the government's theory of prosecution ran afoul of the First Amendment. In prosecuting Alfred Caronia, a former sales representative for a pharmaceutical company, the government had construed the FDCA's misbranding provisions to prohibit and criminalize the promotion of off-label drug use. The *Caronia* Court vacated Caronia's criminal conviction for "mere off-label promotion" by "constru[ing] the FDCA

²⁴ 131 S.Ct. 2653 (2011).

²⁵ See *id.* at 2675-76.

²⁶ See *id.* at 2678.

²⁷ 703 F.3d 149 (2d Cir. 2012).

as not criminalizing the simple promotion of a drug's off-label use by doctors because such a construction would raise First Amendment concerns."²⁸ Accordingly, both the *Sorrell* and the *Caronia* opinions raise significant questions regarding the extent to which FDA may permissibly restrict manufacturer dissemination of off-label information.

Revised Draft Guidance is too restrictive

The Revised Draft Guidance sets forth separate criteria for safe harbors applicable to scientific or medical journal articles,²⁹ scientific or medical reference texts,³⁰ and clinical practice guidelines.³¹ In general, this description of the safe harbors is helpful and the effort to distinguish between different types of scientific publications is much appreciated. However, there are three big areas in which improvements could be made.

The first is lack of clarity. Safe harbors are most useful when they are clear and, as a result, easy to interpret and administer. In many respects, the safe harbors articulated in the Revised Draft Guidance fit this description. In others, however, the lack of clarity is a significant shortcoming. For example, the Revised Draft Guidance states that a scientific or medical journal article should be disseminated with a "comprehensive" bibliography.³² It is easy to imagine disagreements regarding whether or not a particular bibliography is sufficiently comprehensive. This difficulty is further exacerbated by the repeated admonitions that a company should not excerpt, highlight, or characterize an article, suggesting that time and effort must be invested rounding the bibliography out with references on off-topic subject matter that is not relevant to the clinical use at issue. A similar challenge is presented by the recommendation that an article should not be "characterized as definitive of the weight of credible evidence . . . if it is inconsistent with the weight of credible evidence."³³ One can easily imagine intense disagreements about both which evidence is "credible" and how it should be appropriately weighed.

The second is a lack of flexibility. In addition to clarity, a safe harbor's effectiveness is much enhanced if it is flexible enough to practically accommodate real world application. One aspect of the Revised Draft Guidance that presents challenges in this respect is the repeated effort, in various forms, to prevent "cherry picking" (*i.e.*, to prevent the proponent of a particular unapproved use from misleading and opportunistically highlighting only supportive evidence which ignoring contrary information). To prevent this, the Revised Draft Guidance states that an article should not be "marked, highlighted, summarized, or characterized by the manufacturer, in

²⁸ See *id.* at 160.

²⁹ Revised Draft Guidance at 7-10.

³⁰ *Id.* at 10-14.

³¹ *Id.* at 14-17.

³² *Id.* at 8.

³³ *Id.*

writing or orally, to emphasize or promote an unapproved use.”³⁴ The problem with this overly rigid approach is that it fails to reflect the realities of physician practice. With many conflicting demands on their time, most doctors simply will not be inclined to review potentially voluminous, complicated articles and reference materials without any input regarding what is important about them. The requirement that efforts to streamline or excerpt submitted materials go no deeper than a complete chapter, in the case of reference texts,³⁵ or a complete section, in the case of CPGs,³⁶ only worsens this problem of “burying the news.” This particular requirement also seems arbitrary, as one can easily imagine both situations in which submission of an entire chapter or section is obscuringly over-inclusive and situations in which it is misleadingly under-inclusive.

The third is insufficient guidance regarding the key issue of timeliness. Indeed, the only instance in which the issue of timeliness is raised at all is when the Revised Draft Guidance states that, to be considered “trustworthy,” CPGs must be “reconsidered and revised when important new evidence warrants modifications of recommendations.”³⁷ How soon after new evidence is revealed, however, is not specified. Should the new evidence be incorporated immediately or as soon as reasonably practicable, or is incorporation of the time of the next pre-scheduled periodic update sufficient? This issue is arguably even more important with regard to the disclosure of significant risks or safety concerns associated with unapproved uses – a timeliness concern that impacts all of the covered publication types, not just CPGs.

Specific sections

- *Prohibition on distribution at “promotional” events* – The Revised Draft Guidance states that scientific or medical journal articles “may be distributed at medical or scientific conferences in settings appropriate for scientific exchange,” but “should not be distributed in promotional or exhibit halls or during promotional speakers’ programs.”³⁸ The distinction being drawn here between “settings appropriate for scientific exchange” and “promotional speakers’ programs” is not clear. The reality is that line between “scientific exchange” and “promotion” is blurred at most modern pharmaceutical conferences. There is nothing inappropriate about this because there is broad overlap between the two functions. Truthful, non-misleading “scientific exchange” can be a very powerful and effective form of promotion. Consequently, PPTA suggests that the Revised Draft Guidance should focus on ensuring the scientific publications in support of unapproved uses are put in appropriate context rather than relying on highly subjective characterizations of informational forums.

³⁴ *Id.* at 9.

³⁵ *Id.* at 12.

³⁶ *Id.* at 16.

³⁷ *Id.* at 15.

³⁸ *Id.* at 8.

- *Disclosure of nature and amount of author's financial interest* – The Revised Draft Guidance states that when an author of a scientific or medical journal article has a financial interest in, or has received compensation from, a manufacturer, the manufacturer should disclose “the nature and amount of any such financial interest of the author or compensation received by the author from the manufacturer.”³⁹ Because the primary interest here is to provide the reader with a basis for evaluating the objectivity of the author's work, PPTA believes that simple disclosure of the fact that the author has a financial interest, or received compensation, is sufficient. Requiring disclosure of the exact nature and amount of the compensation delves unnecessarily into the author's private terms of employment without providing the reader with additional benefit. It also imposes an unnecessary burden on the manufacturer representative wishing to make use of the article, who must now investigate the terms of the author's contract before passing along the reference. This requirement could also result in unintended commercial consequences for both authors and manufacturers, who would potentially need to adjust their business practices to account for the additional transparency regarding research and consulting fees.
- *Disclosure of significant risks and safety concerns* – The Revised Draft Guidance states that a company distributing a scientific or medical journal article should disclose “[a]ll significant risks or safety concerns associated with the unapproved use(s) of the manufacturer's product(s)” discussed in the article.⁴⁰ PPTA believes that this is a well advised and important requirement, and supports its inclusion in the Revised Draft Guidance. However, the Association also notes that, by specifically requiring a manufacturer to identify the unapproved use for purposes of disclosing risks and safety concerns, while simultaneously prohibiting the manufacturer from identifying the unapproved use for promotional purposes – by, for example, marking, highlighting, summarizing, or characterizing a scientific or medical journal article, orally or in writing⁴¹ – FDA appears to be engaging in the precise sort of content discrimination that the Supreme Court's *Sorrell* opinion warned against.⁴² To remove this significant vulnerability to legal challenge, and to protect the hard work embodied in the Revised Draft Guidance, PPTA strongly recommends that FDA remove the proposed restrictions on characterizing, highlighting, or otherwise identifying unapproved uses from the safe harbor criteria applicable to all forms of publications covered by the current document.

³⁹ *Id.* at 10. See also *id.* at 12 (same requirement for scientific and medical reference texts) and 16 (same requirement for CPGs).

⁴⁰ *Id.* at 10. See also *id.* at 12 (same requirement for scientific and medical reference texts) and 16 (same requirement for CPGs).

⁴¹ *Id.* at 9.

⁴² See *Sorrell*, 131 S. Ct. at 2667.

Conclusion

PPTA appreciates the opportunity to provide these comments on the Revised Draft Guidance and looks forward to continued work with FDA on its efforts to address questions and issues related to the distribution of scientific and medical information reflecting unapproved or uncleared uses. PPTA welcomes from FDA any questions regarding these comments and/or requests for additional information.

Thank you for your consideration.

Respectfully Submitted,



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