Plasma Protein Therapeutics Association

Date: October 24, 2007
Reference No.: FASC07066

The Honorable Edward Kennedy
United States Senate
Washington, DC 20510

The Honorable Michael Enzi
United States Senate
Washington, DC 20510

RE: Discussion Draft on the Wholesale Distribution of Prescription Drugs

Dear Senators Kennedy and Enzi,

On behalf of the Plasma Protein Therapeutics Association ("PPTA"), I am writing to provide you with comments and suggestions on the discussion draft you have circulated regarding the wholesale distribution of prescription drugs. As an association deeply committed to the health and safety of the patients it serves, the following recommendations are intended to ensure the supply of Food and Drug Administration ("FDA") approved, plasma-based and their recombinant analog therapies ("plasma protein therapies") for use in the United States are insulated from malefactors in the distribution channel. PPTA supports Congressional efforts to provide FDA with the authority to implement a uniform national standard for product serialization and track-and-trace technologies to protect these lifesaving therapies, which are primarily used by fragile patient populations for the duration of such patients' lives, from efforts by some to counterfeit, adulterate, or otherwise tamper.

PPTA is the association that represents the manufacturers of plasma protein therapies. PPTA members produce more than 80 percent of the plasma protein therapies for the U.S. market and more than 60 percent of such therapies for global consumption. These therapies, which include albumin, blood clotting factor, alpha-1 antitrypsin, and intravenous immunoglobulin ("IVIG"), are used to treat a variety of orphan diseases and serious medical conditions. As you may know, Medicare beneficiaries requiring IVIG are experiencing some access difficulties. According to the Assistant Secretary for Planning and Evaluation ("ASPE") of the United States Department of Health and Human Services ("HHS"), IVIG distributed in a secondary channel is a factor in these access difficulties but also has raised concern regarding the integrity of the IVIG distribution channel.[1]

Many believe IVIG is already more susceptible to counterfeiting because it is a high value drug used to treat life-threatening diseases, so its growing presence in this

[1] *See* OFFICE OF THE ASS'T SEC. FOR PLANNING & EVALUATION, U.S. DEP'T OF HEALTH AND HUMAN SERV., ANALYSIS OF SUPPLY, DISTRIBUTION, DEMAND, AND ACCESS ISSUES ASSOCIATED WITH IMMUNE GLOBULIN INTRAVENOUS (IGIV), at viii (2007) [hereinafter "ASPE Report"].

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

secondary channel is of great concern to PPTA and its members.[2] According to FDA, if a drug like IVIG is counterfeited or diverted to a secondary distribution channel and stored or handled improperly, it may have dire consequences for patients.[3] In response to this threat, PPTA and its member companies have taken appropriate action, including "reducing the number of distributors to a small number of authorized distributors and restricting their sales to healthcare providers only in their contracts."[4]

A single remedy to secure the distribution channel against counterfeit, diverted, subpotent, substandard, adulterated, misbranded, or expired drugs, however, does not exist, so all parties in the channel must be vigilant in their efforts to protect the integrity of the products which move through the channel. For example, PPTA members have significantly increased their efforts to ensure the safety and availability of life-saving plasma protein therapies. In order to facilitate this goal, PPTA's North American Board established a Channel Integrity Task Force ("CITF") in December 2006. After careful consideration, the CITF recently recommended that PPTA amend its existing *Code of Ethics* to address the responsibility of PPTA member companies to ensure the integrity of plasma protein therapies throughout the distribution channel.

Because of the complex distribution system of prescription drugs, especially specialty products such as plasma protein therapies, PPTA agrees that several layers of safety are necessary to ensure patients continue to receive therapies that are safe and effective. The distribution process is a complex system that may include multiple transactions of the same product before it reaches the consumer. The existence of secondary distribution channels can greatly increase the number of transactions endured by a single drug, which increases the risk of mishandling, faulty storage, mislabeling, tampering, compounding, and counterfeiting of the drug.[5]

In 2005, FDA stated the number of investigations involving counterfeit drugs had increased more than 90 percent from 2003 to 2004.[6] As such, recent efforts by FDA to combat counterfeit drugs have focused on securing the distribution channel through the enforcement of drug pedigree requirements. After some unsuccessful recent legislative efforts to expand existing FDA authority, President George W. Bush signed into law the Food and Drug Administration Amendments Act of 2007 ("FDAAA") (Pub. L. 110-85 (2007)) on September 27, 2007. Among other things, the FDAAA calls for FDA to

---

[2] *See* FOOD AND DRUG ADMINISTRATION, U.S. DEP'T OF HEALTH AND HUMAN SERV., COMPLIANCE POLICY GUIDE 160.900, PRESCRIPTION DRUG MARKETING ACT – PEDIGREE REQUIREMENTS UNDER 21 CFR PART 203 (Dec. 2006) [hereinafter "FDA Pedigree Guidance"]; *see* NATIONAL ASSOCIATION OF BOARDS OF PHARMACY, NATIONAL SPECIFIED LIST OF SUSCEPTIBLE PRODUCTS (Dec. 2004), *at* http://www.nabp.net (last visited October 11, 2007).

[3] *See* FDA Pedigree Guidance, *supra* note 2.

[4] ASPE Report, *supra* note 1 at 2-29.

[5] Verisign White Paper Beyond Pedigree: The Role of Infrastructure in Pharmaceutical Supply Chain

[6] Combating Counterfeit Drugs: A Report of the FDA (May 2005)

promulgate regulations to prevent counterfeit drugs and establish a national pedigree standard.

The discussion draft you have circulated is a much more comprehensive approach and an even better first step than the FDAAA in securing all pharmaceuticals and biologicals, including plasma protein therapies, in the distribution channel. PPTA looks forward to working with you to develop a sound piece of legislation that takes into consideration the technological hurdles associated with manufacturer compliance with both product serialization and tracking technologies, including the eventual linkage of such technologies to an interoperable health information technology system database.

I. Background

On April 22, 1988, President Ronald Regan signed into law the Prescription Drug Marketing Act ("PDMA") (Pub.L. 100-293, 102 Stat. 95). Congress enacted the PDMA primarily to protect the public from substandard, ineffective, and counterfeit drugs by establishing new safeguards for the distribution of prescription drugs and samples of such drugs.[7] Specifically, the PDMA amends the Federal Food, Drug, and Cosmetic Act to:

> "(1) require State licensing of wholesale distributors of prescription human drugs under Federal guidelines that includes minimum standards for storage, handling, and recordkeeping;
>
> "(2) ban the reimportation of prescription human drugs produced in the United States, except when reimported by the manufacturer or for emergency use;
>
> "(3) ban the sale, trade, or purchase of drug samples;
>
> "(4) ban trafficking in or counterfeiting of drug coupons;
>
> "(5) mandate storage, handling, and recordkeeping requirements for drug samples;
>
> "(6) require practitioners to request drug samples in writing;
>
> "(7) prohibit, with certain exceptions, the resale of prescription human drugs purchased by hospitals or health care facilities; and
>
> "(8) set forth criminal and civil penalties for violations of these provisions."[8]

[7] *See* FDA Pedigree Guidance, *supra* note 2.
[8] *See* Letter from Daniel L. Michels, Director, Office of Compliance, CDER, FDA and Thomas S. Bozzo, Director, Office of Compliance, CBER, FDA to Regulated Industry and Other Interested Parties (Aug. 1, 1988).

Although Congress finally promulgated the final rule implementing the statue on December 3, 1999,[9] the FDA had twice delayed the effective date of 21 C.F.R. §§ 203.3(u) and 203.50 – two pedigree provisions in these regulations – until 2006.[10]

Section 203.50 requires "unauthorized distributors," defined as those distributors who do not have "an ongoing relationship with a manufacturer to sell or distribute its products,"[11] to provide purchasers with a "statement identifying each prior sale, purchase, or trade of such drug."[12] Such pedigree must be traceable to the first sale by the manufacturer.[13] Section 203.3(u) defines "ongoing relationship" to include "a written agreement between manufacturer and distributor under which the distributor is authorized to distribute the manufacturer's products for a period of time or for a number of shipments."[14] This regulation does not, however, require manufacturers and authorized distributors of record to provide a pedigree.[15] This distinction notwithstanding, the FDA's Anti-Counterfeit Task Force has been encouraging all parties in the distribution channel to voluntarily adopt electronic track and trace technology. While PPTA agrees with ASPE that unauthorized distributors are driving the secondary distribution channel for IVIG,[16] it greatly appreciates the efforts of the task force.

In a 2004 report, *Combating Counterfeit Drugs, A Report of the Food and Drug Administration*, the FDA's Anti-Counterfeit Task Force recommended that those in the distribution channel adopt reliable track and trace technology, such as Radio Frequency Identification ("RFID"), by 2007. FDA believes that RFID technology could serve two purposes: (1) as an anti-counterfeit measure and (2) as an electronic track and trace system to go above and beyond pedigree requirements.[17] In 2006, the FDA's Anti-Counterfeit Task Force issued a supplemental report that recommended that the agency fully implement regulations related to the PDMA. This subsequent report also continued to emphasize that the use of e-pedigrees using electronic track and trace technology, including RFID, would provide an additional layer of safety to the U.S. drug supply.[18]

One week after the repeatedly delayed pedigree regulations went into effect on December 1, 2006, the United States District Court for the Eastern District of New York

---

[9] *See* 21 CFR § 203.1 *et seq.*
[10] Combating Counterfeit Drugs: A Report of the FDA (June 2006)
[11] 21 C.F.R. § 203.3(bb) (2007).
[12] 21 C.F.R. § 203.50(a) (2007).
[13] *See id*.
[14] 21 C.F.R. § 203.3(u) (2007).
[15] *See generally* 21 C.F.R. § 203.50 (indicating only unauthorized distributors are subject to pedigree requirements); *see* FDA Pedigree Guidance, *supra* note 2.
[16] *See* ASPE Report, *supra* note 1 at 2-30.
[17] Combating Counterfeit Drugs: A Report of FDA (2004)
[18] FDA Press Release on Anti-Counterfeit Task Force Report (June 2006)

granted a preliminary injunction in *RxUSA Wholesale v. HHS* to prohibit FDA from implementing a two portions of 21 C.F.R. § 203.50. Specifically, the injunction enjoins FDA from requiring that the pedigree begin with the original sale by the manufacturer, and from specifying that lot numbers and container sizes be included on a pedigree.[19] Unauthorized distributors must still supply a pedigree that indicates either the manufacturer or the last authorized distributor of record that handled the drug.[20] Such pedigree must still contain the dates of the listed transactions and the names and addresses of all parties to those transactions.[21]

Because of these difficulties in enforcing these regulations, the FDAAA should provide FDA with some authority to develop even stronger pedigree regulations that will eliminate some of the current issues. Specifically, this new law requires FDA, within 30 months, to establish standardized numerical identifiers to be applied at the prescription drug at the point of manufacturing and repackaging at the packet or pallet level. The FDAAA also requires FDA to implement a standard for track and trace technologies, which may include RFID, nanotechnology, and encryption technologies. In developing these standards for product serialization and track and trace technologies, FDA must not only work with other federal agencies, but also stakeholders, including the manufacturers, distributors, and pharmacies.

This law differs greatly from the legislation introduced during the 109th Congress by Senator Chuck Schumer (D-NY) and Representative Steve Israel (D-NY). That legislation, also known as Tim Fagan's Law, would have required a pedigree to begin with the manufacturer of the drug and continue throughout the wholesale distribution to the pharmacist who intends to sell the drug. [22] Additionally, those bills would also have granted the FDA broad recall authority, allowing the agency to pull products if it determines that a drug intended for human use would cause serious, adverse health consequences or death.[23] As discussed earlier, the discussion draft you have circulated provides a much more comprehensive approach than either the FDAAA or Tim Fagan's Law.

II. Principles Supported by PPTA

As you now know, plasma protein therapies are biologicals that require special handling, storage, and shipping conditions. Congress and the FDA must consider the complexity of these lifesaving therapies when considering a law directed at comprehensive, national prescription drug distribution, and the subsequent regulations

[19] *See* FDA Backgrounder re: *RxUSA Wholesalers, Inc. v. HHS*
[20] *Id*.
[21] *Id*.
[22] H.R. 2345 and S. 1978 (2005)
[23] *Id*.

promulgating such law. PPTA member companies are committed to protecting the public health against counterfeit, misbranded, or adulterated versions of their therapies. As such, PPTA supports the following principles with respect to the establishment of a federal prescription drug pedigree requirement:

- The establishment of a uniform, national prescription drug pedigree standard that preempts existing and future State laws and regulations with regard to pedigree.

- The implementation of a manufacturer generated unique numerical identifier applied to each prescription drug package, as defined as the unit of sale in which a drug may be received by a pharmacy or other entity authorized to acquire or possess prescription drugs.

- Manufacturer discretion in the development and implementation of product identity and tracking technologies.

- The creation of a federal prescription drug wholesaler licensing requirement that preempts existing and future State laws and regulations with regard to wholesaler licensing. Any entity distributing plasma protein therapies must not only maintain a wholesale license in good standing, but also be an authorized distributor of the manufacturer for whose product it is distributing.

In transitioning toward full compliance, PPTA believes a national standard may be satisfied with a manufacturer's detailed packing list, invoice, or comparable document at the start of the pedigree, subsequent distributor electronic or paper pedigree, and manufacturer maintenance and Web site publication of its list of authorized distributors as called for by your discussion draft.

A. PPTA Supports the Establishment of a Uniform National Pedigree Standard:

PPTA supports the establishment of a viable, uniform national pedigree standard that would preempt the plethora of existing and future state laws. Currently, biologics manufacturers, including plasma protein therapy fractionators, are having difficulty navigating the complex and competing individual state pedigree and serialization mandates established by the individual state legislatures. PPTA member companies are specifically concerned with the some of the burdensome and seemingly overbearing laws scheduled to go into effect in California.[24]

PPTA is supportive of the discussion drafts inclusion of federal preemption in the critical areas of pedigree and serialization. Moreover, PPTA believes that positive aspects of federal preemption will be maximized if the drafters of this discussion draft

[24] *See* discussion, *infra* section III.C.

consider an immediate preemption of state law, in contrast to the draft's provision that will implement preemption only after the long drawn-out process of final FDA regulations are commenced. Plasma protein therapy manufacturers believe that compliance with state regulations and then switching and reconfiguring to federal standards would be inefficient and time-consuming, therefore an immediate implementation of federal preemption would secure a single efficient accelerated adoption of appropriate new-track-and trace systems.

Furthermore, PPTA is concerned with the provision in the discussion draft that permits states to apply for an opt-out to federal preemption if the state can show the exemption is "required by compelling local conditions" and "would not unduly burden interstate commerce". PPTA believes that allowing states to opt-out of federal preemption would encourage the proliferation of a myriad of state requirements that would ultimately decrease the significance of a viable federal preemption standard of which the intent of the bill is to create. Moreover, if many states are exempt from federal preemption there could be disruptions to the supply chain that could threaten and endanger patient safety. To this end, PPTA strongly recommends that the opt-out provision be stricken from the bill. If however, Congress moves forward and allows states to seek different federal standards by showing "compelling local conditions" that "would not unduly burden interstate commerce", we would support the establishment of higher thresholds for those exemptions. For example, states petitioning for an opt-out to federal preemption must establish, through empirical evidence, that the benefit of the exemption to supply chain integrity significantly outweigh the added costs to manufacturers, distributors, and patients; and that a petitioning state establish that the exemption will not lead to any inconsistent result in the process by which pedigrees are passed under the federal framework.

B. PPTA Believes Development and Implementation of Product Identity and Tracking Technologies Should Be Left to the Manufacturers Discretion:

PPTA supports the discussion draft's technology neutral interoperable standards-based approach that allows for manufacturers to implement product-appropriate technological solutions. As you may know, plasma protein therapies are complex biologicals that require unique storage, packaging and shipping methods that could be sensitive to differing technologies in electronic pedigree platforms. Moreover, while there are new promising technologies such as 2-D barcode and Radio Frequency Identification (RFID) tags, there are serious questions on how these specific technologies will affect the stability of complex plasma protein molecules. Furthermore, there are certain concerns that metal and liquids in product vials may interfere with RFID devices and risk jeopardizing the integrity of the system. It is often said in the drug and biological manufacturing industries that that 'one size does not fit all', this term of art specifically rings true to plasma protein therapies. To this end, there is not a single technological solution to counterfeiting, but many available technological solutions. Thus, PPTA believes that the manufacturers of lifesaving complex plasma

protein therapies should be afforded the discretion in providing product appropriate technologies that will accommodate their unique biological make-up.

III. Technical Comments

A. Sec. 2: Transitional Provisions to Assure Safety of the Wholesale Distribution of Prescription Drugs (p. 1-7):

- Manufacturer's Packing List: The proposed framework sets forth a requirement that the packing list contain the numerical identifier once the regulations in Sec. 4 become effective. This provision is redundant with the proposed pedigree framework outlined in the bill and PPTA believes it should be removed.

- Storage Conditions Verification: The statement on page 4 (B)(ii) that the drug was stored under proper conditions is excessive since drugs have a range of recommended storage temperatures, and stability tests show that drugs can remain stable at higher temperatures for varying durations. The bill should be clarified that packing the product for a short duration in a warehouse where it exceeds the recommended storage temperature range, but not the higher temperature for which stability data exists is not a violation.

B. Sec. 3: Regulation of Wholesale Distributors of Prescription Drugs (p. 8-21)

- PPTA supports the draft bill's creation of a federal prescription drug wholesaler licensing requirement that preempts existing and future State laws and regulations with regard to wholesaler licensing.
- PPTA believes that any entity distributing plasma protein therapies must not only maintain a wholesale license in good standing, but also be an authorized distributor of the manufacturer for whose product it is distributing.

C. Sec. 4: Unique Standardized Numerical Identifiers (p.21-23):

- *Definition of "Package":* The discussion draft requires the Secretary to issue regulations to establish a standardized numerical identifier "unique to each package." However, it is unclear at what level of packaging the numerical identifier should be applied. For instance, the California pedigree law defines the requirement at the lowest level, but is not clear if that is a carton or a vial/bottle. This language, as well as the reference to numerical identifiers on page 4, should be clarified to mean the packaging or carton received by the pharmacy, rather than the individual vial or pill box. To clarify that the standardized numerical identifier must only be applied to the trade container or shipping carton, we propose that the language state: "unique to each package in which a drug may be received by a pharmacy or other entity authorized to acquire or possess prescription drugs." PPTA also has

that same concern with the use of the term "discrete package" at p. 22 lines 4-5 and 11-12; again we propose language identical to what is proposed above to clarify the level at which the identifier is applied.

- *Repackaging:* If a repackager chooses to modify the packaging by taking a unit-level product (tablet or vial) out of the carton, then the repackager should be required to apply a separate numerical identifier on the unit level which clearly associates that identifier to the numerical identifier of the unit from which it was derived.

D. Sec 5: Prescription Drug Identification and Tracking System (p.23-27)

- *Harmonize Timeframes*: Page 23 provides 18 months for the implementation of the numerical identifier, which appears to be similar to the California law. However, page 26 provides for the Secretary to propose rules for track and trace in 12 months from enactment, to have final rules in 24 months and to be in effect in 3 years. The timeline for numerical identifiers should be harmonized with that for track-and-trace, particularly since track & trace and serialization applications will require significant renovations to packaging lines and production systems thereby necessitating the longer lead times. Changes to company packaging lines and adoption of the necessary information handling systems based on final rules will require more than one year for most companies to accomplish.

  New requirements passed in H.R. 3580 mandate that, “not later than 30 months after the date of the enactment of the Food and Drug Administration Amendments Act of 2007, the Secretary shall develop a standardized numerical identifier to be applied to a prescription drug at the point of manufacturing and repackaging at the package or pallet level sufficient to facilitate the identification, validation, authentication, and tracking and tracing or the prescription drug”. The new law also requires international harmonization, to the extent practicable, for standardized numerical identifiers.

E. Sec. 6: Additional Anti-Counterfeiting Provisions (p. 27-28):

- *Pedigree Framework Sufficient:* This section, which sets forth additional anti-counterfeiting provisions, is no longer necessary because this proposal sets forth a comprehensive pedigree framework.

F. Sec. 9: Notice of Counterfeit Drugs (p. 30):

- *Counterfeit Reporting:* This section requires the manufacturers (and others) to "immediately report" (1) a counterfeit drug and (2) instances where entities can't validate the "transaction history" of a drug by verifying the numerical identifier with the database. Industry already regularly reports counterfeit drugs to the FDA and we believe that this provision may have unintentional negative consequences. We

are concerned that small wholesalers, hospitals and pharmacies may not be able to validate if they do not have adequate systems at the time of implementation. If these drugs are good, but returned, this could adversely affect company Returns policy with risk/loss. If the goal of the provision is to improve the efficiency of electronic validation systems, we feel that these issues should be worked out directly through interaction with business partners without the FDA as an intermediary. We believe this section should either be eliminated, or reporting requirements should be established in regulation rather than statute.

IV. Conclusion

PPTA urges Congress and the FDA to give consideration to the technological hurdles associated with manufacturer compliance with both product serialization and tracking technologies, including the eventual linkage of such technologies to an interoperable health information technology system database. PPTA member companies are committed to ensuring the safety and efficacy of the therapies they produce, and remain vigilant and dedicated to anti-counterfeiting and product tracking initiatives in the distribution channel.

Sincerely,

Julie A. Birkofer
Vice President
PPTA North America