

May 19, 2008
Reference: FDAA08010

VIA WEB & USPS

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, RM 1061
Rockville, MD 20857

SUBJECT: Docket No. FDA-2008-N-0120, Standards for Standardized Numerical Identifier, Validation, Track and Trace, and Authentication for Prescription Drugs

Dear Sir or Madame:

The Plasma Protein Therapeutics Association (PPTA) is pleased to respond to the Food and Drug Administration's (FDA) Request for Comments on *Standards for Standardized Numerical Identifier, Validation, Track and Trace, and Authentication for Prescription Drugs* [hereinafter, "Request for Comments"]. PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies. Our members provide 60 percent of the world's needs for Source Plasma and protein therapies. These include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat complex 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.

Securing the pharmaceutical supply chain continues to be one of PPTA's highest priorities. PPTA applauds FDA's unrelenting efforts to combat the counterfeit drug problem in America. The creation of FDA's Counterfeit Task Force and corresponding Anti-Counterfeit Drug Initiative Workshops demonstrate the Agency's commitment to working with all parties in the supply chain to solve this problem. These initiatives coupled with work completed by legislators, manufacturers, distributors, and pharmacists have significantly decreased the chance of counterfeit drugs from entering the U.S. market, making America's pharmaceutical supply chain one of the safest in the world.

Section 913 of the Food and Drug Administration Amendments Act (FDAAA) (Public Law 3580) requires FDA, within 30 months of enactment, to develop standards for the identification, validation, authentication, and tracking and tracing of prescription drugs along with identifying and validating effective technology carriers. Congress passed this

law to provide FDA with a stronger tool in preventing counterfeit, diverted, subpotent, substandard, adulterated, misbranded, or expired drugs from reaching consumers.¹ PPTA supports specific product identification that provides companies with the ability to track and trace product in the distribution channel. However, it is important to note that there is no single solution for solving the counterfeit drug problem and a multi-layered approach with many different components is necessary.

Manufacturers know their products and business practices best and are in the best position to determine the correct anti-counterfeit methodologies or technologies and tailor an implementation accordingly. To be successful, any guidance developed by FDA in furtherance of such technology or technique must recognize this. FDA needs to clearly define the standard and requirements but the guidance needs to consider the spectrum of pharmaceuticals and biologic products that will be impacted and provide reasonable measures for adaption.

For example, not all pharmaceuticals are distributed in a traditional wholesale channel. PPTA represents a small specialized portion of the drug manufacturing industry. Most plasma protein therapies are distributed through small specialty distribution channels that require specific temperature controls. Due to the uniqueness of our products and its supply chain not all anti-counterfeit technologies can be adopted.

PPTA understands adoption of uniform standards throughout the supply chain is of paramount importance. However, flexibility in data carriers for implementation of those standards is needed. Flexibility in regards to implementation of a defined standards will permit members of all supply chains to adapt over time and continue the ability of PPTA members to bring life-saving therapies to the patients who need them. Moreover, to implement meaningful standards, FDA must ensure that the standards will work in a global market. Developing standards that are not compatible internationally will only further complicate the supply chain, possibly causing more opportunities for counterfeiters to infiltrate the system. Lastly, it is important that FDA adopt clear requirements that will alleviate the need for individual States from adopting diverging legislation in this area. PPTA commends FDA for seeking input from parties in the supply chain and for recognizing the need to address some of these issues within the Request for Comment.

In the Request for Comment, FDA solicits information on five specific areas with approximately 75 questions delineated. In previous comments to Docket FDA-2008-N-0120, PPTA requested an extension of time to allow interested parties the necessary time to answer the questions with substantive information. PPTA recognizes that FDA is under time constraints connected with FDAAA. However, PPTA reiterates that the short-time frame to present comments limits the ability to respond appropriately to the

¹ FDAAA § 505D(a)

questions. Nonetheless, PPTA is committed to further reducing counterfeit drugs and is pleased to have the opportunity to respond to the specific questions in the Request for Comment.

A. Standard Numerical Identifier

1. Characteristics

- a. The standard numerical identifier could contain a combination of recognizable characteristics and random codes. Recognizable characteristics, like the National Drug Code (NDC), could facilitate product identification in the United States. However, this would not assist in implementing a global solution. Use of the Global Trade Identification Number (GTIN) that incorporates the NDC number and serial number would provide a global solution. A model implementation which incorporates both recognizable numbers at the item level and randomized identifiers at the shipping level, such as case or pallet, would be beneficial.
- b. From an information technology standpoint, common headers for certain drugs, like biologics, would be valuable. As stated previously, plasma protein therapies are a unique subset of biologics that must be maintained under specific conditions. Providing a common header for certain therapies will assist in ensuring the necessary shipping and storage requirements are met. Additionally, certain data carrier technologies are not compatible with biologics or may have detrimental effects on the product. A common header could theoretically help identify those products that cannot carry those technologies. For instance, the effect of RFID on biologics is still unknown. PPTA understands FDA completed a study regarding the effects of RFID on biologics. However, this study remains unpublished. PPTA recommends FDA make this study publicly available to allow industry the opportunity to review and evaluate RFID appropriately.
- c. To ensure numbers are unique and not duplicated, the numerical identifier should be composed of a code for the manufacturer, the product, the lot number, the expiration date, coupled with a serialization code assigned by the manufacturer. GS1, a standards setting organization, has developed a standard consistent with this format and architecture.
- d. Applying the standard numerical identifier on more than one location, possibly package and pallet level, may be problematic and costly with no measurable benefit to the overall integrity.

- e. The numerical identifier should be both machine and human readable, in the event there are problems with the data carrier, the numerical identifier could still have utility.
- f. The lot number and/or batch number should be part of the numerical identifier at the unit and case level.

2. Standards

- a. GS1 has developed standards that could serve as the standard numerical identifier, such as those established for the SGTIN, described below.
 - 1. SGTIN can identify unique items at the unit or retail level as well as at case and carton levels. It is composed of a GS1 assigned company prefix and item reference GTIN, combined with a serial number. Additionally, GS1 can incorporate the NDC within the GTIN. A portion of supply chain stakeholder companies have begun to adopt the GS1 technology standards, however to prevent any inadvertent forestalling of progress, FDA needs to definitively prescribe in detail any standards which may diverge from those already set forth by GS1.
 - 2. Currently, it is unclear whether there is consensus by stakeholders on the adoption of standards and this has frustrated implementation for all supply chain members. Clarification or guidance from FDA in this area would facilitate common adoption strategies, potentially leveraging what already exists.
 - 3. At this time, the SGTIN standard appears to be the only standard that would encompass all the necessary components to meet the requirements of FDAAA.
 - 4. At this time, PPTA is unfamiliar with other standards.
 - 5. PPTA views the adoption of existing standards or at least innovating within these standards as the most appropriate way for the Agency to proceed.
 - 6. At this time, PPTA cannot provide comments on whether this standard has been adopted by other countries. However, given the trend toward global implementation of GS1 standards, other countries may likely follow suit.
- b. PPTA lacks information with regard to this sub-part and therefore cannot respond fully. PPTA does not know the specifics of standards under development but has recognized the efforts of GS1 and its subsidiary EPC Global in developing new standards to meet the needs of the

pharmaceutical industry. For instance, EPC Global created a pedigree standard to meet the requirements of the California legislation.

- c. Elements that should be included in the standardized numerical identifier are the GTIN (containing the product's NDC number), lot number, expiration date, and a unique serialization number.
 - d. PPTA lacks specific information relevant to the biologics industry on the actual use of standardized numerical identifiers and therefore only offers the following general information. There has been relatively no implementation of a standardized numerical identifier of prescription drugs within the U.S. supply chain. PPTA is aware that small pilot programs may exist within certain companies or regions but no large scale implementation program exists. This is likely due to lack of stakeholder consensus as to the appropriate standard. Until the federal government provides guidance on this issue, there will be little movement forward.
 - e. As stated previously, PPTA remains concerned about certain data carriers for standardized numerical identifiers; in particular, RFID. PPTA advocates that any standard recommended by FDA be flexible on technology and allow for updates and changes as more information becomes available.
 - f. PPTA urges FDA to seek input from foreign regulators on these issues. For example, Japan adopted a standard for bar code labeling of ethical drugs and the European Union sought comments on this issue in "Public Consultation in Preparation of Legal Proposal to Combat Counterfeit Medicines for Human Use". Moreover, certain European countries have adopted national standards. Consulting with foreign regulators is essential as U.S. pharmaceuticals operate in a global market.
3. Economic Impact
- a. Barcodes (2D or linear) are standard practice in the industry; however, the application of standardized numerical identifiers within such barcodes has not been widely adopted due to lack of requirement for such identifier as well as initial and ongoing operational constraints associated with implementation. Nonetheless, there is a relatively low cost associated with application of bar codes versus other data carrier technologies. However, design, development, validation, and implementation of the information technology systems add considerably to the cost. In addition, other technologies are more expensive.
 - b. Industry research has indicated that representative costs associated with equipping an existing packaging line for one product for application and use of standardized numerical identifiers ranges from \$500,000 - \$1.5

million. The broad spectrum of cost is directly related to the data carrier selected for implementation and similarly, it is the data carrier that also drives ongoing maintenance costs. For instance, technologies such as RFID can range from \$.20 to \$.50 per RFID tag compared to negligible ongoing or incremental costs associated with barcode technology.

- c. PPTA can make no comment with regard to costs which may be associated with updating systems to conform to new or changing standards for the track and trace of prescription drugs. At best, this would be determined on a case-by-case basis considering several variables such as the technology solution implemented; product type impacted and associated validation/qualification activities.
- d. The benefit to using a standardized numerical identifier would be the ability to track and trace product in the supply chain and identify products more quickly and efficiently that could be counterfeit, diverted, subpotent, substandard, adulterated, misbranded, or expired.

4. Harmonization With Other Countries.

- a. Please see comment A. (2) (f) above.
- b. Please see comment A. (2) (f) above.

B. Standards for Validation

1. PPTA seeks clarification from FDA on what the term “validation” means as the term is used in Section 913 of FDAAA. Specifically, PPTA seeks clarity as to whether validation of process, design, or product is required.
2. Please see comment B. (1) above.
3. Please see comment B. (1) above.
4. Please see comment B. (1) above.
5. Please see comment B. (1) above.
6. Please see comment B. (1) above.

C. Standards for Track and Trace

1. Technologies exist for track trace of products; however PPTA is not aware of whether the use of these technologies is driven by formal or otherwise adopted standards. For example, certain logistics companies such as FedEx, UPS, and DHL use track and trace standards to deliver packages. It is important to note that these companies control the package within one entity and are able to set their own standards and processes.

- a. PPTA is unable to address the remaining questions in this sub-part with regard to any existing industry standards as it lacks information as to the existence of any such standards. Moreover, existing practices may not be driven by standards, but rather by individual company business models.
 - b. Please see comment C. (1) (a) above.
 - c. Please see comment C. (1)(a) above
 - d. Please see comment C. (1) (a) above.
 - e. Please see comment C. (1) (a) above.
 - f. Please see comment C. (1) (a) above.
 - g. Please see comment C. (1)(a) above.
2. At this time, PPTA is unfamiliar with the intricacies of track and trace standards. However, PPTA acknowledges that GS1 has developed a traceability standard that may be of use in the development of standards for the entire pharmaceutical supply chain.
- a. PPTA is unable to fully comment on the scope and applicability of track and trace standards.
 - b. It is unclear to what extent, if any, stakeholder consensus has been achieved. However, GS1 represents a comprehensive array of prescription drug product stakeholders, including manufacturers, wholesalers, pharmacies and technology vendors.
 - c. Based on the amount of stakeholder input industry has provided to GS1 in furtherance of its standards developments process, FDA should give considerable deference to such standards, leveraging where appropriate the benefits of the work that has already been accomplished.
 - d. At this time, PPTA is unaware of any other existing standards for the track and trace of prescription drugs.
 - e. PPTA lacks information to address this question and therefore makes no comment.
 - f. PPTA lacks information to address this question and therefore makes no comment.
3. PPTA is aware of additional standards being developed by GS1 and EPC Global, but does not have specific knowledge of their timeline for completion.

4. Elements considered essential to the development of track and trace standards and/or regulations are: (1) a standardized numerical identifier established by federal regulation and which has a hierarchical level of application commensurate with a given product's perceived or actual risk of counterfeiting or diversion; (2) an electronic pedigree which utilizes the numerical identifier; (3) standard data elements required to establish a drug's pedigree; (4) provisions for the management of pre-existing inventory during periods of transition following the introduction of new or amended standards; (5) recognition of the need for neutrality in any established requirements with regard to data carrier selection and implementation; (6) clarity as to what authentication requirements would exist for transactions involving pharmaceuticals; (7) provisions, such as the use of inference, which would address the line-of-sight limitations of certain data carriers (e.g. those based on barcode technology) and not unnecessarily limit or discourage their use; (8) provisions which recognize and provide clear definition of the different supply chain constituents who will hold varying and different responsibilities under this regime; and (9) pre-emption of state-based requirements pertaining to pharmaceutical supply chain security.
5. The implementation of track and trace for prescription drugs in the U.S. supply chain is technically feasible. However, based on the complexity of individual company implementation programs and a lack of standards or at least consensus on standards, PPTA is unable to provide a timeline. Representative costs have been outlined in Section A. (3)(b) above. Once standards exist, an informed assessment of impact, cost, and associated timelines can be meaningfully determined. Moreover, any complex issues need to be addressed and specifically determined by FDA before implementation would be successful. One such issue that requires FDA determination is inference, which is an essential element of a workable track and trace system. Inference permits the substitution of aggregate-level (e.g., pallet or case) tracking for item-level tracking provided that certain additional considerations for product and package integrity are maintained throughout distribution. Allowing inference ensures implementation will proceed unimpeded with bar code technology at the package level. If inference is not allowed, then each pallet and case would need to be opened and manually scanned, resulting in an intense amount of manual labor that would slow the supply chain down, as well as, unnecessarily increase manual manipulation of product. It is critical that the supply chain continue to function safely and efficiently ensuring patients have access to the therapies they need.
6. For data integrity reasons, serialization and track and trace data should reside with each entity. Any data storage requirement needs to ensure privacy of all parties in the supply chain. At this time, PPTA is unable to provide substantive comments.

7. PPTA lacks information to address this question and therefore makes no comment.

D. Standards for Authentication

1. PPTA does not fully understand what the term “authentication” means as it is used in Section 913 of the FDAAA. Specifically, PPTA requests clarification as to whether the term refers to standards pertaining to overt/covert and forensic technologies that can identify products as being authentic or whether it has some other meaning.
2. Please see comment D. (1) above.
3. Please see comment D. (1) above.
4. Please see comment D. (1) above.
5. Please see comment D. (1) above.
6. Please see comment D. (1) above.

E. Prioritization

1. Prioritization of standards should be considered a mandatory first step in the standards setting process. Consistent with other aspects of FDA regulation, a risk-based approach is warranted. FDA’s first priority should be the development of a standard for the standardized numerical identifier. The use of a unique standardized numerical identifier at the unit of sale level will be the only way to move forward with a track and trace standard. This standard will be the building block for all other standards. Next, FDA’s priority should be for a clear and definitive statement of the requirements for track and trace. FDA needs to define at what level track and trace will be implemented. Without such defined guidance, industry is unable to implement or move forward. Moreover, the FDA’s allowance or disallowance of inference is critical in the design of the system and costs. Inference would enable the use of 2D matrix bar code at the package level.
2. The standard for the standardized numerical identifier should be done first and then move onto the development of standards for track and trace.

Conclusion

The supply chain for prescription drugs is highly complex. Developing a standard to meet the requirements of FDAAA will be an enormous undertaking. Successfully achieving the goals of this legislation requires definitive specification of requirements, adoption of a harmonized approach, a review of the technologies, a design of the

business processes and information management, and perhaps most importantly, a phased approach to implementation. This does not mean conducting pilot programs. A phased implementation would entail that each phase implements, tests, and refines components and processes that will be used in the subsequent phases. Each phase builds upon the successes and lessons of the prior phase. Such a phased approach must be developed and defined in order to achieve a successful tracking and tracing system in the U.S. pharmaceutical supply chain.

As stated above, PPTA commends FDA's continued efforts to combat the proliferating counterfeit problem. PPTA believes that with FDA's guidance and enforcement capabilities coupled with industry's continued vigilance and use of new technologies, America's drug supply will remain the safest in the world. PPTA appreciates the opportunity to comment and looks forward to working with FDA on this important issue. Should you have questions regarding these comments or would like to discuss these issues further, please contact me at the Association. Thank you for your consideration.

Sincerely,



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