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2/23/2006

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

RE: **Anti-Counterfeit Drug Initiative Workshop and Vendor Display; Docket No. 2005N-0510 (71 Fed. Reg. 1759; January 11, 2006)**

Dear Sir or Madam:

We commend the U.S. Food and Drug Administration's leadership role in conducting the recent workshop to pursue additional measures to secure the integrity of the U.S. pharmaceutical supply chain. Additionally, as a leading provider of products and services supporting the healthcare industry, we thank you for the opportunity to comment and provide our insight regarding issues surrounding RFID, E-pedigree and the Prescription Drug Marketing Act (PDMA).

Our detailed comments are attached. If you have any questions or need anything further, please feel free to contact me at 614/757-7101 or e-mail at steve.reardon@cardinal.com.

On behalf of Cardinal Health, we thank you for considering our comments and for the Agency's efforts in addressing the important issue of pharmaceutical supply chain integrity.

Sincerely,

Stephen J. Reardon
Vice President
Quality & Regulatory Affairs

SJR/kdnm
Attach.

A. *Implementation of RFID*

1. What incentives are needed for more rapid and widespread adoption of RFID in the U.S. drug supply chain? How can these incentives be achieved?

Cardinal Health believes that the fastest, safest and easiest way to secure the supply chain is by purchasing direct from the manufacturer and distributing those products directly to our customers. Financial incentives to support the capital investment would help speed adoption, but RFID adoption will not further secure the supply chain until there have been more collaborative pilot programs to improve accuracy and read rates. Incentives might also be directed toward development of common, distributed database architecture, which would be necessary for RFID to be used effectively in the supply chain.

2. What are the current obstacles to widespread adoption of RFID in the U.S. drug supply chain? How can these obstacles be overcome?

The major obstacles to the widespread adoption of RFID include the following issues:

- Participation by all members of the supply chain: significant benefits between trading partners will not be achieved until industry works together to resolve business and commercial issues, develop standards and build the required infrastructure.
- Serialization of all products by the manufacturers including generics: the benefits of RFID, such as improved inventory management, recall and returns management, data sharing and enhanced supply chain security will only be realized when all products are tagged.
- Data management and data sharing: need to determine what information will be captured, how the information will be captured and stored, which trading partners will have access to the data and under what circumstances, and how the data will be accessed.
- Technology that is reliable, affordable and available: will enough tags be available at reasonable cost and will the tag failure rate (defective tags) be at an acceptable level so as to not cause significant disruption of warehouse operations?
- Read rate accuracy greater than 99%: a high level of accuracy is necessary in order to maintain warehouse efficiencies. For example, inaccurate reads during the order filling process would require an exception process whereby shipping totes would have to be reopened, misread product removed and reread or replacement product picked, if a read cannot be obtained.
- Industry wide standardization: technology standards, including the frequency to be used for readers and tags, are needed to ensure interoperability of tags and readers across business partners in the supply chain. Product identification data standards are needed to determine what information will be encoded on the tag.
- Privacy: need to ensure that the use of RFID on pharmaceutical products is implemented in such a way as to not provide the opportunity for a violation of patient privacy.

- Tagging of proteins and biologics: the impact of RF on product stability for these items is unknown at this time.
- Readability for creams, packages with foils and liquids: liquids and metal packaging can present interference problems, making data difficult to read.
- Two sets of processes, technologies, and infrastructure will need to be in place everywhere in the supply chain during the phase-in process until 100% of product is tagged. Wholesale distribution centers will have to be designed to efficiently handle tagged and untagged product as it flows through the supply chain.
- Lack of industry focus on a single approach could lead to fear of early obsolescence of RFID investments

3. What is FDA's role in further facilitating adoption of RFID across the drug supply chain?

The FDA's participation as process facilitator is essential in the adoption of RFID by the industry. The agency must play a leadership role on issues such as standardization; clearing hurdles associated with labeling; privacy concerns; consumer education; data management with respect to storage and access; and processes regarding who must read the tags, when and where in the supply chain they must be read, disposition of product with failed tags and how and when tags are decommissioned. Additionally, FDA needs to issue guidance regarding the impact of RFID on all types and dosage forms of prescription drug product.

4. What is the timetable for widespread adoption of RFID across the drug supply chain, with and without additional incentives?

A definite timeframe is difficult if not impossible to predict. Cardinal Health is thoroughly investigating RFID as a promising technology for the future. We recently launched a comprehensive pilot program to tag, distribute and track product through our distribution network to customers. While we see many benefits of RFID, a number of challenges, such as the obstacles identified in the above question two, must be addressed and solved by all participants in the supply chain for this to be an effective solution. Before widespread adoption can occur, in addition to overcoming the aforementioned obstacles, a standard real-time e-commerce system that is significantly beyond current deployments would have to be designed, software vendors would have to create products to implement it, and trading partners would have to integrate it into their current business practices and systems.

B. *RFID Standard Setting*

1. **Who should set the standards for RFID? Currently we are aware of the efforts of only one organization, EPCglobal, to develop standards for the use of RFID in the drug supply chain. Are there other entities within the United States or abroad that are also developing standards for the use of RFID for the drug supply chain?**

Cardinal Health currently supports the work of EPCGlobal in their effort to collaboratively establish standards that can enable efficient RFID-based e-commerce systems. These standards serve to focus and align the pharma industry on a specific approach which will reduce the fear companies have of making investments that become obsolete too fast. However, these standards are currently incomplete. Important EPCGlobal standards that are in the works but not yet finalized and adopted are:

- EPC-IS (EPC Information Server)
- ePedigree document schema
- EPC Discovery Services

It would be dangerous to require the use of a technology before the standards are complete and proven to be viable. The fact that these standards are not yet complete is one of the largest reasons pharmaceutical companies are not making greater use of RFID today.

2. **Role of FDA**

- **Is there a role for Federal leadership by FDA to advance the standard setting efforts? What is that role?**

Uniformity and issue resolution before widespread adoption are essential to the success of this supply chain transformation and participation by the FDA as a process facilitator can help ensure it. Cardinal Health encourages FDA to support ongoing standards-setting work conducted by EPCGlobal by actively participating in the Healthcare and Life Sciences Business Action Group. By participating in the standards-setting process, FDA can help with establishment of those standards and best practices. For example, FDA could help mitigate the problem of RFID read rates by agreeing that 100% tag reading is only necessary once while the product is in the possession of a member of the supply chain. This would allow supply chain participants to infer tags at receiving as long as all tags were read and authenticated at some later time prior to shipment to the next stop in the supply chain. This approach allows patient safety and supply chain track and trace to remain fully intact. Such an approach, with agreement by the FDA, would help accelerate adoption because it would help solve the wholesaler problem of low read rates at receiving.

- **Is there a role for other Federal entities, such as the Drug Enforcement Administration or the Department of Defense?**

The DEA, in concert with the FDA, needs to play a role in developing standards and providing policy guidance with respect to the tagging of controlled substances.

- **Should standards remain voluntary? Why?**

Yes. Properly created standards will focus the industry on a single approach which will drive efficiencies and lead to widespread adoption without mandates. This is why the collaborative approach to the standards-making process is so important.

C. *Specific Drug Supply Chain RFID and E-pedigree Issues*

1. Mass Serialization (the incorporation of unique identifier number on each drug package)

- **What numbering conventions currently are being used or considered for mass serialization?**

EPCGlobal has formed a serialization working group focusing on creating a recommendation for a numbering standard to be used on the RFID tag or on an electronic track & trace system. This process has made great strides forward this year. Cardinal Health encourages the FDA to participate in this process.

- **Should there be a single numbering convention or are different conventions compatible?**

Cardinal Health believes that a single, standard numbering convention should be supported by the FDA and the industry. Multiple numbering conventions would add unnecessary complexity, cost and risks of incompatibilities and errors.

- **Should the national drug code (NDC) be part of the unique identifier or should the identifier be a randomly generated number? Concerns have been raised that use of the NDC raises privacy issues. What is the extent of these concerns and how should they be addressed?**

Currently, the industry spotlight is on EPCGlobal's EPC as the serialization standard. Cardinal Health supports this approach. EPC is an international standard that enables worldwide product identification. It is also flexible enough to allow the creation of a subset of product codes and serial numbers for use within a specific locality, like the United States, using the NDC as part of the code, for

example. While this is a capability of the EPC standard, Cardinal Health believes that the NDC should not be incorporated into the EPC for the following reasons:

- Privacy

A growing percentage of drugs are packaged in a way that does not require repackaging by a pharmacist. RFID tags on these products, if not destroyed or disabled by the pharmacist, could be read by unauthorized individuals while the drug is in the possession of the patient. If the NDC could be extracted from the EPC, the patient's privacy would be violated.

- DEA Controlled Substance Regulations

21 CFR 1301.74(e) requires DEA registrants, when shipping controlled substances, to employ precautions to guard against in-transit losses. If the NDC could be extracted from the EPC, the product could be identified, thus potentially violating this DEA requirement.

- Information Security

Using only a combination of the manufacturer's ID and a randomized serial number for the EPC number (no product-specific code like the NDC) would require a network connection to a database to make any use of the EPC. This database connection provides the mechanism necessary to secure the information associated with the EPC and control access to that information.

Cardinal Health expects manufacturers to continue to apply the existing NDC barcodes to all drug packages, even after RFID tags are applied to them. This existing NDC barcode can be used in the future as it is today. Therefore, the NDC does not need to be part of the unique identifier.

A proposal does exists in the industry to use an encryption mechanism within the EPC number itself to hide the NDC on an RFID tag. Cardinal Health believes that this proposed technique is less desirable than simply removing the NDC entirely because of the unacceptably high processing time necessary to decrypt the code on each read, the complexity of maintaining a large number of current encryption keys, and the breadth of the exposure when a key is inevitably obtained by an unauthorized person.

- **What is the timetable for widespread mass serialization for prescription drug products, with and without additional incentives?**

Cardinal Health recommends a phased-in approach for tagging by pharmaceutical manufacturers of prescription drug products which are more likely to be counterfeited. This approach would enhance supply chain security for these high risk products as well as help industry invest in RFID and expand their experience with this technology which may help solve some of the current known problems associated with item-level tagging.

2. Universal Pedigree Fields

- **Are there logical concerns or barriers to passing a pedigree for a drug that moves from one State to another with different pedigree requirements?**

A lack of uniformity and standardization with state pedigree and technology requirements creates issues around compatibility, interoperability of software solutions, pedigree elements, data management/sharing, warehousing efficiencies and cost which could all contribute to the inability to move prescription drugs in interstate commerce. This lack of uniformity and standardization is evident when comparing current pedigree requirements in Florida, California and Indiana, all of whom presented at the FDA Counterfeit Drug Task Force Public Workshop. Florida requires that the wholesaler start the pedigree, which can be paper or electronic, and has specific design and security requirements for the electronic pedigree system. California requires an electronic pedigree that must be initiated by the manufacturer, but doesn't go beyond specifying that the pedigree must be electronic. Indiana adopted the "normal distribution" concept which allows for distribution without a pedigree when product goes from the manufacturer to a wholesaler to a pharmacy. Three states with three different requirements for pedigree.

- **Would a universal pedigree alleviate these concerns or barriers? How?**

Cardinal Health believes that the fastest, safest and easiest way to further secure the supply chain is by purchasing direct from the manufacturer and distributing those products directly to our customers. However, if pedigree laws continue to be enacted, harmonization of state legislation is critical, as well as FDA and industry involvement in the development of standards to support e-pedigree implementation.

- **What common fields/information are the most important in a pedigree? Why?**

In an effort to create uniformity and standardization regarding pedigree content, the below listed data elements, identified by the Unified Pedigree Task Force as those necessary to create a complete chain of custody for a drug product, are those deemed most important:

- Legend Drug Name
- Strength
- Dosage Form
- Container Size
- Manufacturer
- Lot number, Quantity
- Invoice quantity, date

- Sold to name, address
- Ship to name, address
- Purchase date and invoice number
- Recipient name, signature
- Authenticator name, signature
- Telephone number
- E-mail address
- License number
- Expiration date
- Digital signature

These data elements are those necessary to effectively identify and trace the movement of a drug product through the supply chain and allow for the affirmative verification that each transaction listed on the pedigree has occurred.

- **How can a universal pedigree be achieved?**

Cardinal Health believes that the fastest, safest and easiest way to further secure the supply chain is by purchasing direct from the manufacturer and distributing those products directly to our customers. However, if pedigree legislation is going to be enacted, harmonization of state legislation is critical, as well as FDA and industry involvement in the development of standards to support implementation. Cardinal Health recommends that the Unified Pedigree Task Force be reconvened to facilitate this process.

3. **Data Management and Security**

- **One issue that has been raised is whether the data/information should be stored in one central database or if a distributed approach (where each stakeholder's system exchanges information with other systems) should be used. Can/should the pedigree information be passed and authenticated using either model? If some stakeholders subscribe to a central database and others use a distributed approach, can the pedigree information still be passed and authenticated?**

The database should not be centralized but distributed with each participant owning and holding pedigree documents that they are legally bound to hold and present. A distributed system would enable each supply chain participant to control the security and access of this data.

- **What types of encryption or other data security measures are available to ensure the authenticity of the information being passed and digitally signed?**

Cardinal Health supports the use of Public Key Infrastructure (PKI) and the Federal Information Processing Standards (FIPS) to ensure the authenticity and non-reputability of information that is passed in electronic pedigrees. Digital certificates should be issued to, and controlled by, the corporation or the site and not individuals.

- **What measures can be taken to secure the database themselves in either the central database or distributed approach?**

Cardinal Health supports a distributed database model to hold information about the chain of custody of pharmaceutical products. One of the reasons for this is the higher security of a distributed database. Each site where data is stored would be protected by multiple layers of security. A security breach at one point in the distributed database would expose only a small fraction of the total data. A security breach of a central database would likely expose all data. Additionally, Cardinal Health favors a standards-based approach to data/information storage and access. EPCGlobal is working on the formalization of their EPC-IS (Information Server) standard which implements a distributed database model. We believe that it is vitally important that a single approach be established for the pharmaceutical industry and at this time we believe that those standards that EPCGlobal is working on are the preferred approach. Data handling, security, and access controls are all a part of those planned standards. We recommend that FDA support the efforts of EPCGlobal in this area.

PRESCRIPTION DRUG MARKETING ACT

A. *1999 Final Rule*

1. Small Business Impact

How has the potential impact of the 1999 rule on small businesses changed since the 2001 public meeting?

Cardinal Health no longer trades in the secondary market for prescription drugs and is not in a position to comment.

2. Delay of The Effective Date

- **If the delay of the effective date is not extended, how will implementation of the rule affect primary and secondary wholesalers? Would it impact the distribution of drugs to smaller**

retail outlets or rural communities? Will secondary wholesalers have access to the information they need to meet the pedigree requirements?

- **What is the regulatory significance of the fact that the current federal pedigree requirements apply only to wholesalers who are not authorized distributors of record? Please explain**

- **Should the delay of the effective date be further extended? If so, how long should it be extended? Why?**

- **If the delay of the effective date is not extended, would the 1999 rule ensure that there is effective track and trace capability to combat drug counterfeiting? If not, why?**

Cardinal Health endorses implementing the final PDMA rule. We believe that the fastest, safest and easiest way to further secure the supply chain is by purchasing direct from the manufacturer and distributing those products directly to our customers. The ADR concept within the PDMA encourages this approach by allowing the ADR who purchased the product direct from the manufacturer to further distribute the product without providing a pedigree while requiring other wholesale distributors, ADR and non-ADR, who purchase from the first ADR to provide and maintain appropriate pedigree documentation. The rule will allow for the efficient functioning of the pharmaceutical supply chain where direct-from-manufacturer purchasing occurs, while still providing for the appropriate chain of custody documentation to be maintained when this is not the case.

3. Minimum Standards for Wholesaler Licensing

- **The PDMA required FDA to issue minimum standards for wholesaler licensing. ((21 USC 353(e)(s)(A)), codified at (21 CFR 205.3)). These standards were adopted by the states and incorporated into state law. How effective are these standards?**

Cardinal Health believes that one of the significant key elements necessary for securing the supply chain is tougher licensing standards. Cardinal Health would recommend that the current minimum FDA standards for licensure be strengthened to ensure that only legitimate, qualified distributors are licensed to handle prescription drug products.

B. *Adoption of E-pedigree Across the Drug Supply Chain*

1. What is the status of developing standards that allow for interoperability of e-pedigree solutions across the drug supply chain?

State pedigree deadlines are ahead of the standards-making process that is necessary to produce supply-chain interoperability between vendor e-pedigree software solutions. As a result, there is a risk of e-pedigree document incompatibilities that would inhibit the normal and proper movement of pharmaceuticals through the supply chain.
Additionally, as a point of clarification, e-pedigrees are not a standard requirement in states' pedigree legislation. Cardinal Health believes the solution to counterfeit activity revolves around tightening the supply chain through direct-from-manufacturer purchasing and tougher licensing standards. However, in order to comply with the varying pedigree laws in the most efficient manner possible, Cardinal Health is investing in e-pedigree solutions to facilitate the management and sharing of data throughout the supply chain.

2. To what extent are stakeholders using e-pedigree?

Cardinal Health has made significant investments and continues to focus on identifying and implementing required business modifications to support the use of e-pedigree where required by law. At this time, Cardinal Health is in the initial phases of implementing e-pedigree solutions in order to meet state regulatory requirements such as in Florida and California.

3. If you are not using an e-pedigree program now, do you anticipate having this capability in the future? If so, when do you plan to use e-pedigree?

The implementation and use of e-pedigree is being driven by state mandated pedigree requirements such as in Florida and California. Cardinal Health continues to work toward meeting the July 1, 2006 Florida deadline which presents several significant challenges in making the necessary business process modifications including data capture at point of receipt and shipment, quality control, inventory control and return goods processing . However, because of a lack of standards and uniformity, additional obstacles such as data management/sharing issues and interoperability of software solutions will continue to exist beyond the implementation date.

4. What is the experience to date of interoperable e-pedigree solutions across the drug supply chain?

So far there is no known use of e-pedigree solutions—outside of closed pilots—where interoperability issues would be exposed. Cardinal Health understands that EPCGlobal's typical standards-making process includes interoperability testing and we anticipate and trust that will occur in the next few months. Once completed, software vendors will have to address any issues exposed and re-deploy their products in supply chain organizations.

By that time, these organizations will have already begun creating pedigrees in preparation for the Florida deadline. There is a risk of insurmountable incompatibilities resulting from this situation.

5. Paper to E-pedigree Transition

- **Discuss the feasibility of a paper and e-pedigree system co-existing across the drug supply chain.**

Any type of paper pedigree system would have significant negative impact on the efficiency of the highly automated distribution systems currently in place due to the sheer volume of prescription drugs that flow through the supply chain. A paper system is incompatible with our modern pharmaceutical distribution system and would break this system resulting in the inability to move the volume of pharmaceuticals necessary to maintain public health. The modern distribution system requires a high degree of automation for its very operation. The insertion of a paper system for tracking inventory movements (pedigrees) is incompatible with the volume of pharmaceuticals moved in today's supply chain because it would nullify the use of many of those automation systems.

- **Can the authenticity and validity of the pedigree be maintained in such a system? How can this be done?**

First, a point of clarification, e-pedigree does not equal RFID nor does an e-pedigree system require RFID. However, an e-pedigree system would be made more efficient with RFID or mass serialization. Without mass serialization, the authenticity and validity of the pedigree relates only to the transactions listed on the pedigree itself. The pedigree can never be associated to a specific bottle of a particular drug only to a specific lot number which can be associated to thousands of bottles. Without mass serialization, a specific bottle of a particular drug cannot be authenticated.

- **What capabilities would be needed for such a system?**

All manufacturers must apply a unique identifier to all drugs. There must be industry wide standardization; technology that is reliable, widely available, and affordable; all participants in the supply chain must participate in order for this to be an effective solution and read rate accuracy over 99%. The largest pharmaceutical wholesalers combined distribute approximately six million eaches of product to their customers on a daily basis. A read rate accuracy of anything less than 99.99% would result in hundreds of thousands of unread tags and presumably unsaleable product which could contribute to product shortages and have a negative impact on operational efficiency in that each failed read would have to be handled as an exception to normal warehouse processes.

- **Please provide cost estimates for the minimal equipment and infrastructure needed for members of the supply chain to accept and pass a paper pedigree.**

A paper system is incompatible with our modern pharmaceutical distribution system and would break this system regardless of the cost, resulting in the inability to move the volume of pharmaceuticals necessary to maintain public health. The modern distribution system requires a high degree of automation for its very operation. The insertion of a paper system for tracking inventory movements (pedigrees) is incompatible with the volume of pharmaceuticals moved in today's supply chain because it would nullify the use of many of those automation systems. As mentioned above, the largest wholesalers combined distribute approximately six million eaches of product to their customers on a daily basis. Potentially, this could be six million paper pedigrees per day as well.

- **Cost estimates for use of e-pedigrees?**

Cardinal Health has made significant investments and continues to focus on identifying and implementing required business modifications to support the use of e-pedigree in order to meet the July 1, 2006 Florida deadline. Estimated costs to bring just two distribution centers on line are in excess of seventeen million dollars. These costs include more than fourteen million dollars for the below listed transitional items and approximately three million dollars for annual ongoing costs.

- E-pedigree system software (third-party or internal build)
- New computers necessary to execute the E-pedigree software
- New database software and storage systems to hold pedigrees
- New or upgraded network infrastructure to accommodate the increased throughput requirements to construct and maintain pedigrees
- Integration of the e-Pedigree software into existing systems
- Modification of business processes and their associated system changes to create, track and maintain pedigrees
- Changes and upgrades to e-commerce software and hardware to accommodate the exchange of pedigree documents with trading partners.

6. **What is the timetable for widespread adoption of e-pedigree across the drug supply chain, with and without additional incentives?**

E-pedigree, alone, is not an effective solution to combat counterfeit activity. E-pedigree does not equal RFID nor does an e-pedigree system require RFID. However, an e-pedigree system would be made more efficient with RFID or mass serialization. Without mass serialization, the authenticity and validity of the pedigree relates only to the transactions listed on the pedigree itself. The pedigree can never be associated to a specific bottle of a particular drug only to a specific lot number which can be associated to thousands of bottles. Without mass serialization, a specific bottle of a particular drug cannot be authenticated. Cardinal Health believes that the fastest, safest and easiest way

to further secure the supply chain is by purchasing direct from the manufacturer and distributing those products directly to our customers. Under this model, there would be no reason for widespread adoption of e-pedigree. Where required by law, widespread adoption is dependent on the availability of standards, including a unified pedigree standard across states as well as the industry developing a consistent rollout plan for the serialization of products and the implementation of the corresponding infrastructure and systems. Additionally, since industry is preparing to implement e-pedigree in only one state, a timetable for widespread adoption would be difficult to estimate.