A mob descended on the big conference room at the Food and Drug Administration (FDA) White Oak campus in Maryland on May 8 and 9. It wasn’t a revolt, but change was in the air and the crowd was on edge. The FDA, at Congress’s direction, was considering how to implement a new law that requires manufacturers, wholesalers, and pharmacies to trace drug products as they move through the distribution chain. The law kicks in on January 1, 2015. Between now and then, and even afterward, some degree of turmoil will enfold pharmaceutical industry players as they figure out how to comply with the new regulatory regime.

During the May 8 morning session, while discussing the provisions of the Drug Supply Chain Security Act (DSCSA) that Congress passed last November,1 Connie Jung, RPh, PhD, the FDA official running the workshop, looked up at the audience, stopped, and said, “I hear some snickering.” The unhappy murmuring was directed at some of the drug product tracing provisions in the Pharmacy Distribution and Security Act (PDSA), one of the two titles in the DSCSA. The FDA held the two-day workshop to get industry input on the draft guidance it is scheduled to release in November. It will guide drug manufacturers, wholesalers, and pharmacies on how to comply with the first wave of DSCSA requirements. Starting January 1, 2015, manufacturers will have to give wholesalers compliance information, either on paper or electronically, in the form of transaction information, transaction statement, and transaction history (TI/TS/TH). That will be a single document called the “DSCSA compliance document.”

The wholesaler, who is next to receive ownership, makes some changes and sends a clean DSCSA document to the pharmacy. If a secondary distributor is part of the chain, he passes along information, too. The pharmacy must verify the document, determining that the drugs it has received are the drugs that originated with the manufacturer. The pharmacy has to record the information, save it for six years, and be able to retrieve it in the event that the manufacturer or the FDA asks the pharmacy to search for “suspect” or “illegitimate” products, which the law defines. Moreover, the pharmacy cannot even accept a product unless it comes with a transaction history.

From January 1, 2015, to November 27, 2017, products will be traced by their lot numbers. After that, manufacturers must imprint unique serial numbers on each unit-level product and package, introducing a much more accurate tracing and tracking system.

Law’s Idiosyncrasies Complicate Compliance

The law contains some idiosyncrasies that will complicate implementation in some instances. For example, the pharmacy’s life will be a little easier when it receives ownership from a primary wholesaler: McKesson, AmerisourceBergen, or Cardinal. In that instance, the primary wholesaler will send a paper DSCSA document to the pharmacy. The TI/TS/TH will be on the document, but the lot number won’t be included. It will be printed on the container of 500 pills or on whatever unit container arrives.

The primary wholesalers were exempted from providing lot numbers because they argued to Congress that it isn’t feasible. That is because they put many different products with different lot numbers into a single container destined for a single pharmacy. The lot numbers are printed on each package. They cannot be individually scanned and uploaded to a database because of the limitations of technology. So considerable manual effort is needed to record those lot numbers and tie them to the DSCSA document. The wholesalers did not want to do that, and they implied there would be a cost impact if they were forced to do so.

Congress, in its wisdom, or in acceding to political pressure, exempted them, thinking that counterfeits are not an issue when the primary wholesaler buys directly from the manufacturer. So why worry about lot numbers? There are not going to be any counterfeits in that shipment. Of course, the absence of lot numbers on documentation makes it harder for the pharmacy to trace a particular container in the event of a recall.

Pharmacies also buy from secondary distributors, who can sometimes provide a product when the primary wholesaler cannot get it. The law says secondary distributors—the broken link in the chain where counterfeits typically come in—do have to send the pharmacy the lot number, but it does not have to be included in the paper documentation. That is a problem for pharmacies, says Susan Pilcher, Vice President of Policy and Regulatory Affairs for the National Community Pharmacists Association:

This is of great concern to the pharmacy community, particularly in light of the fact that during the PDSA discussions about this topic, there were some secondary wholesalers that indicated that the only manner in which they planned to “pass” the lot number information was on the actual bottle of medication that was being sold to the pharmacy. In order to be able to comply with the record retention requirement of the law and in order to respond to requests for information from the FDA, it is essential that pharmacies receive this information in a single document—whether in paper or electronic format.

---

Mr. Barlas, a freelance writer based in Washington, D.C., covers topics inside the Beltway.
New U.S. Drug Tracing Regimen Stirs Concern

Initial Tracing Based on Lot Number

The DSCSA defines the elements that need to be included in each of the three items of the TI/TS/TH. For example, a TI must contain 10 pieces of data, including the lot number and the National Drug Code for each item in a particular shipment. Until November 2017, when manufacturers are required to print a unique serialized identifier on each unit package of each drug, the key piece of the TI is the lot number. If a manufacturer sells one million saleable items in a year, and it has 10 packaging events during that year where 100,000 units are packaged, then 10 different lot numbers would be assigned, and that number would be printed on each saleable unit (sometimes on a syringe, for example) packaged during that “event,” on the container the unit is packaged in, on the carton it is shipped in, and often on the pallet the carton is placed on.

The system based on lot numbers, however, is leaky. An unscrupulous distributor could purchase 10 cases of legitimate product from a wholesaler. He now has a record of what he received, including the lot numbers. Nothing prevents him from going out and purchasing 40 cases of counterfeit product. When he sells the counterfeit product to the pharmacy, the bad guy simply shows the legitimate document with legitimate lot numbers he received from the primary wholesaler. The pharmacy is none the wiser.

Compliance with DSCSA requirements starts January 1, 2015, for manufacturers and wholesalers, and six months later for dispensers, primarily pharmacies. Those initial requirements will be spelled out in greater detail based on the FDA’s publication of “Standards for the Interoperable Exchange of Information for Tracing of Human, Finished, Prescription Drugs, in Paper or Electronic Format.”

The FDA is supposed to issue that guidance by November. It will specify in more detail than the congressional bill exactly how documentation must be passed, i.e., in what form, and what that document should include. That will give trading partners precious little time to implement the form of their DSCSA compliance document, including getting software systems up and running (unless, of course, they are using paper). Even before the November deadline, the FDA has to issue separate guidance documents on what constitutes a suspect or illegitimate product. Complicating the issue further, the rules will be “draft” standards, meaning their longevity is in question. The final guidance, whenever that appears, may contain changes. Moreover, “guidance” has minimal legal standing. The FDA cannot fine a company for ignoring guidance.

“There is a lot the FDA has to do to stand this up,” says Anne Marie Polak, a director at FaegreBD Consulting, which represents the Pharmaceutical Distribution Security Alliance.

The short window between publication of draft guidance and the need to comply with that guidance explained why uncertainty was the order of the day at the FDA workshop. No one expects the FDA to issue that draft guidance before November, although there were multiple pleas from the audience to do so. The FDA could move more quickly if it had more staff assigned to this very technical task, and/or it had more technical people with knowledge of pharmaceutical industry distribution channels on its roster. But neither is the case. It was clear that the FDA officials writing the guidance have very little understanding of how each player in the distribution chain creates and receives shipping documents, and the differences within various categories of documents.

But perhaps the FDA cannot be faulted for lacking technical understanding. Even members of the audience were flummoxed over terminology and definitions, both regarding aspects of how the DSCSA document would be passed down the line and what form each of the 10 TI items must take. Differences of opinion from sector to sector were clear. For example, is a shipping document created by computer in PDF form and then sent to a trading partner an “electronic,” interoperable document? How many digits should a National Drug Code (NDC) have?

“What does interoperability even mean?” asked one attendee among the many who grabbed the microphone during the free-for-all discussion on the morning of May 9.

Interoperable Tracing: “How” Will Be Difficult

Although a DSCSA document is supposed to be interoperable starting January 1, 2015, only those passed down in electronic format will be … maybe. The format favored by manufacturers and wholesalers is called the Electronic Data Exchange (EDI) Advanced Ship Notice (ASN), sometimes called an 856 document. EDI documents, including the ASN, are based on standards established by the American National Standards Institute. A second alternative is the Electronic Product Code Information Service (EPCIS) method, which is a GS1 global standard. Both are based on standards, so they offer the promise of uniformity within the drug distribution chain. The third option would be an electronic invoice.

The ASN is the tool of choice because it has been around for decades, there are numerous vendors around who can install the system, and it is being used by the major manufacturers and major wholesalers. But it is not used by the minor wholesalers and definitely not by the pharmacies, which could not receive an ASN. Still, the ASN appears to be the best choice, even though it is not structured to include the transaction statement or transaction history, which for now may be recorded in a text field without a standard format. The ASN is an electronic text document passed from manufacturer to wholesaler.

“While electronic is a favored approach, we are going to have to bend the ASN standard, which was never meant for trade history, in order to include previous transaction, and that may get somewhat unruly. EPCIS on the other hand is designed to provide current and past transactions but must be updated to support tracking by lot number and is much less widely used,” explains Bill Fletcher, Managing Partner at PharmaLogic Solutions, LLC.

The GS1 standard calls for the TI to be encoded in a Datamatrix two-dimensional barcode on the carton and the unit dose package. It was developed so that manufacturers can print a unique serial number on each package. The DSCSA requires this by November 27, 2017. Until then, tracing of products is done via the lot number, which, again, is one of the elements of the TI. The current version of GS1 does not allow for inclusion of lot numbers. Version 2.0 will be out this spring or summer. But that will not give manufacturers enough time to test it and incorporate it into their packaging, to the extent that manufacturers are using GS1 tags now (and few are).

Electronic invoices are problematic for a number of reasons. They could be sent in the form of a PDF. But invoices generally
New U.S. Drug Tracing Regimen Stirs Concern

Paper Documents Aren't a Good Option

Of course, a DSCSA document in paper form isn’t interoperable, either, although that is the least of its limitations. Pharmacies may have to log in hundreds of paper invoices a week, since they are not set up to receive ASNs and are not likely to make the investments to be able to do so. Some manufacturers send paper invoices in the form of packing slips with the shipment, in addition to an ASN, or by mail or fax to transfer relevant information to downstream trading partners. These methods are not based on a standard. But, probably for the benefit of their pharmacy customers, manufacturers are likely to send both ASNs and paper invoices with TI/TS/TH. Paper packing slips have considerable shortcomings for pharmacies. They currently do not include the name of the manufacturer who initially owns the product; instead, they include the name of the entity shipping the product. Including both the transaction statement and transaction history will be cumbersome, especially for those trading partners that must transmit this information in a single document. There may be timing issues in cases of split shipments (i.e., portions of a single order shipped separately, possibly on different days), since the packing slip would only be attached to one portion of the shipment.

The paperwork burden is significant, too. Fletcher says that pharmacies could scan paper invoices with transaction information, turn them into electronic PDF documents, and search for particular lot numbers. “They might have some false returns but they could likely find documents with a specific lot number,” he states.

Pharmacies will have two alternatives to keeping paper invoices on the premises. They will be able to avoid having to log them in if they opt to subscribe to a cloud-based data supplier such as TraceLink. It counts eight of the 12 major U.S. drug manufacturers among its clients, all of whom connect to the TraceLink Life Sciences Cloud, using it to exchange their DSCSA documents with trading partners. For customers, there are subscription costs involved, of course. But TraceLink offers the advantage of a single connection to a company’s entire supply network while allowing manufacturers, wholesalers, pharmacies, and others to “talk” to one another in different electronic voices, such as ASN versus EPCIS, with TraceLink enabling each company to use its preferred format. One challenge facing the industry is that there is no common standard, as there is for EDI and EPCIS, for portal-based communications that were discussed as a key to exchanging DSCSA compliance documents with independent pharmacies.

The second alternative is for the pharmacy to pay its wholesalers to store the DSCSA documentation and give the pharmacy access to it if need be. Wholesalers aren’t going to do this for free.

Transaction Elements: “What” Is Complicated, Too

Defining the “how” is probably a bigger challenge for the FDA than defining the “what.” One wouldn’t expect a lot of confusion there given that Congress listed the 10 items to be included in the transaction information.

But Anita T. Ducca, Vice President of Regulatory Affairs for the HDMA, says her members are confused about these elements: “number of containers,” “container size,” and “NDC number.” She adds:

It is illogical and unnecessary for the wholesale distributor to inform the dispenser as to the number of containers of the pharmaceutical it received from the previous owner. Including that detail may even be confusing and counterproductive by distracting the dispenser/purchaser from rapidly identifying other, and far more important, TI information for the customer’s purposes.

PhRMA’s Spurgeon says the “date of transaction” requirement could pose a particular challenge to manufacturers. “Industry relies on countless arrangements with complex and varying contractual terms related to sale, shipment, ownership, and billing and invoicing,” she explains. “A single approach to the term ‘date of the transaction’ that is applicable to every arrangement across the manufacturing industry is not feasible.”

PhRMA wants the FDA to provide manufacturers with flexibility to determine what date to use for the “date of the transaction” as long as the date used is reasonable for a company’s given business arrangements and ensures the ability to establish the relevant chain of control for a product as part of an investigation consistent with the intent of the DSCSA.

Trading partners are also unenthusiastic, to say the least, about passing along a transaction statement. The DSCSA defines that statement as the sender affirming it:

A) is authorized as required under the DSCSA;
B) received the product from a person who is authorized as required under the DSCSA;
C) received transaction information and a transaction statement from the prior owner of the product;
D) did not knowingly ship a suspect or illegitimate product;
E) had systems and processes in place to comply with verification requirements;

continued on page 518
Drug Tracing Regimen Stirs Concern

continued from page 490

F) did not knowingly provide false transaction information; and
G) did not knowingly alter the transaction history.

Primary wholesalers recommend that the FDA permit the phrase “DSCSA compliant” to satisfy the transaction statement requirements. Other, longer statements would create enormous data storage burdens that could significantly undermine the adoption and usefulness of electronic transactions.

Whatever new regimen the FDA imposes will be imperfect in many ways. Aside from the holes that Congress either inadvertently created or did not anticipate, the system’s biggest flaw, perhaps, is that it starts with the manufacturer and ends with the pharmacy. There are no security requirements around the chemicals the manufacturers receive as ingredients for their drugs. Nor does a lot number allow a pharmacy to identify which patient received “suspect” or “illegitimate” drugs.

“Ideally, we would want to find the patient who received a particular drug and tell him or her to stop taking the drug, but the law doesn’t drive to that point,” says Fletcher. “We don’t get a true picture of the lineage of the product, just the middle life. There are many examples of ingredients resulting in harm, and if we must recall all of a drug because we cannot pinpoint the recipient, we impact the health of those who are not at risk by denying them their needed medication.”

REFERENCE