Is Your Serialization Program Complete and Sustainable?

Various considerations can help provide a robust serialization solution based on the FDA's Drug Supply Chain Security Act.

Bill Fletcher
Senior Director, Traceability and Electronic Client Communications
Knipper Health

INTRODUCTION

The FDA's Drug Supply Chain Security Act (DSCSA) deadline was November 27, 2023. The DSCSA requires all pharmaceutical manufacturers and suppliers to serialize individual units and provide electronic track and trace for every product that travels through the supply chain. The DSCSA also includes other requirements that are often not fully understood or implemented. Full implementation of these requirements can be complicated, costly, time consuming, and confusing. Numerous variables need to be considered by developers. Considering and mitigating challenges is important to achieving compliance and success when it comes to promising therapeutics entering today's market.

IMPORTANT CONSIDERATIONS FOR DSCSA IMPLEMENTATION

Given the complexity of serialization and the full set of DSCSA requirements, a deep dive into all operations is necessary to unearth the multitude of factors that must be managed. Thoughtful planning from the onset can help manufacturers avoid significant hardship down the road (**FIGURE 1**).

Labeling and Encoding

Organizations may believe they are ready for serialization because their packages are labeled and serialized. However, it is not uncommon to have symbols, barcodes, or data matrix codes encoded incorrectly, according to GS1 standards. In this instance, the raw information in the code comes through, but it is not parsed out in a way that can be easily interpreted by business systems. While those labels passed inspection from a manufacturer's perspective, they fail as they move further down the supply chain to regional distribution centers or dispensers. Throughout this transition, inconsistencies begin to surface and present a problem for those who are trying to use those very symbols, which are required specifically in the federal law, to pull data into their business systems. For reasons such as this, it is important to have

FIGURE 1: Is your project complete?

- Serialization, is it correctly labeled and encoded?
- Child-to-parent aggregation?
- Traceability documents, EPCIS and alternatives?
- Verification?
- Authorized distributor of record (ADR) verification?
- Suspect product investigation procedures?
- Returns?
- Handling procedures adequately documented?

labels verified by an independent source, such as a logistics provider or 3PL, to ensure correct labeling and encoding.

Child-to-Parent Aggregation

While not specifically required under the DSCSA law, child-to-parent aggregation is necessary as products move through the supply chain to allow receivers to scan a sealed container, such as a shipper case or pallet, and have the system provide the necessary information on all "child" serial numbers enclosed in that container. The information is sent in advance and delivered into business systems. Then, when a pallet is scanned, the receivers know how many items are on the pallet, as well as the serial numbers of all individual products. This saves the industry from having to open every package and scan every item for every shipment, which would be unsustainable. If one level of child-to-parent aggregation is missing in the data exchanged, such as an inner-pack or bundle, then the receiver may not be able to identify the items in the bundle. This means they must unwrap and scan those items.

Traceability Documents

Traceability documents are equally critical. Electronic product code information services (EPCIS) is a global open standard that is common among most midsized and large buyers. It is also used to provide the serialization from contract packages to an organization. The EPCIS is applied across many industries and is not unique to the life science industry. Thus, it could be used in a variety of different ways. The intent of the standard is to track events associated with serialized items throughout their journey, as they travel from their original commissioning all the way down to their ultimate dispensing or destruction.

Adding to the confusion are requirements by some buyers to add information to the EPCIS file that are not required for DSCSA compliance. Some of the optional information has been suggested by industry groups, such as GS1. These include Advanced Shipping Notice (ASN) reference and custody or “ship to” location.

Smaller recipients tend to seek alternatives to EPCIS because they need to receive the serialization data under the federal law but prefer not to pay for a service that stores the serialization for them. They prefer to simply receive the information under the law, which they are obligated to retain for six years, in a portal. But not all portals are the same and many require special training to understand how to obtain needed information or only provide the complete DSCSA compliance document as an EPCIS download that is difficult for them to interpret.

Verification

Verification is yet another important issue. A service that was developed to electronically handle and route information about verification requests is called the verification router service (VRS). Interestingly, many companies have implemented the VRS but have yet to receive a request for verification through the service. This is because both ends of the service need to be set up for the service to work; the requester and responder must both be on the system. Now that everyone is receiving all the serialization, however, they already have access to the data. It will be interesting to see whether the VRS service becomes what was expected or if the industry will accept receiving the serialization with each shipment and simply use that for their own verification. It is assumed that larger wholesalers will likely still want VRS because they routinely take back products and resell them. To do that under the law, they need to verify the serial number, for which VRS can be extremely helpful.

Many companies have expressed that they were fully compliant with the requirement to verify the buyer, proper licensing, etc., only to discover they were not. For example, one company felt strongly that they were performing that type of verification. However, an assessment revealed they had several buyers whose licenses had been expired for well over six months. The organization lacked a clean, robust process for ensuring they had verified the licensing before placing an order. This type of process should be carefully assessed to support compliance.

Suspect Product Investigation Procedures

Many companies assume they have complete sustainable suspect product investigation procedures established, only to learn during investigations, including those by the FDA, that their procedures do not provide enough detail to ensure consistent execution via a repeatable process. In fact, one of the largest wholesalers in the United States received a public warning letter from the FDA because they lacked adequate detail in their standard operating procedures (SOPs) for suspect product investigation. Companies should review their procedures to ensure they contain enough detail so their process can be performed consistently.

Considerations for the process include determination of who collects the report when a suspect product report is received, what information gets recorded, how the investigation progresses, and how the outcome is reported. Another aspect to consider is the time frame of the investigation. The law defines a particular time frame for completing a suspect product investigation. The longer the investigation takes, the more the person with a suspect product begins to become concerned. They may fill out the FDA form 3911 to report it as a suspect product, which will initiate another investigation that can quickly spiral out of control. Thus, it is critical to make sure that suspect product investigation procedures and any other procedures related to DSCSA compliance are judiciously appraised.

Product Returns

Returned product is another common issue. If an order is shipped but then cancelled, it is temporarily out of their custody, meaning out of a company's control. When the product is returned, according to federal law, it must be verified for serial numbers before being restocked and sold again. A robust, detailed process must be in place to ensure consistent processing of returns to comply with the DSCSA law.

Handling Procedures

Handling procedures also require thorough documentation. High-level documents relating to how products are handled and moved through the distribution facility are common, but they lack detail to show that they can be consistently followed and repeatedly executed. As such, handling procedures should be examined to ensure a reasonable review of them would demonstrate reliable implementation and repeatability.

There are several guidance documents from the FDA, Healthcare Distribution Alliance (HDA), and GS1 to help companies navigate the challenges of DSCSA compliance. Proactively researching all guidance is highly recommended to help prevent difficulties in the future.

EXCEPTIONS

There are many exceptions to the DSCSA law. Companies are advised to fully explore the exceptions that impact their business. It is also advised that companies completely document their exceptions to ensure consistent execution (see **FIGURE 2**).

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Global Location Number

Many DSCSA exceptions are data-related issues. While a Global Location Number (GLN) is not required by the DSCSA, it is preferred with EPCIS. The number represents a unique value that is assigned to a physical location or business entity, thereby overcoming various discrepancies such as clerical differences in how an address is entered into a system (e.g., Street vs St.). The GLN can be defined once in the EPCIS

FIGURE 2: Exceptions to the DSCSA law.

- Data issues.
  - Global Location Number (GLN).
  - Master data and global trade item number (GTIN)
  - Shipping details.
  - Required data by buyer in EPCIS. that is not required for DSCSA.
- Buyer receives, but incorrect or no data.
- Label inconsistencies.
- Suspect, recalled or illegitimate.
- Guidance, FDA, HDA, GS1.

file and referred to thereafter so transfers of ownership are unambiguous. Although some businesses decide not to register for a GLN, its low cost and benefits make it an attractive option.

Global Trade Item Number

The Global Trade Item Number (GTIN) is a unique identifier for each trade item of a business. The GS1 standards organization developed a process for encoding a GTIN, in which the first digit represents the package level, followed by the country code, a ten-digit national drug code, and a check digit. The country code 03 represents United States pharmaceutical products. The coding process yields a 14-digit number that can be consistently used to unmistakably identify a product.

Problems arise, however, when the packaging configuration of a product is altered but the GTIN is not changed. Because the GTIN encompasses packaging information, it should be revised to reflect the modification. When it is not amended, everyone further down the supply chain will assume that everything in the package is unchanged from previous shipments. Altering the packaging configuration without updating the GTIN will result in misidentifications, confusion, and potential suspect product investigations. It is always a good idea, therefore, to update the GTIN when making changes to packaging.

Shipping Details

There are many different shipping details that are stored in the EPCIS, some of which are not strictly required for DSCSA. Many companies have extended the information in the EPCIS file to include other information they would like to receive to help manage and process orders. The most obvious of these is the child-to-parent aggregation information. While not legally required, it is still commonly included in the compliance document.

Generally, the EPCIS file's purpose is to comply with the DSCSA. However, it is not strictly used for that intention. Many companies require an advanced shipping notice (ASN) to be in that file, although it is no longer used for DSCSA compliance because it lacks serialization information. It is typical to use an ASN document for normal business purposes, and some companies want to see that reference in the EPCIS to facilitate cross-referencing back to the shipping document.

Another example is the inclusion of who took custody of the product in the EPCIS file. The DSCSA law is about change of ownership and not custody. However, many companies will have direct shipments from a seller to one of their many locations. They want to see, in the EPCIS file, the actual custodian who received it. Again, this transaction information is an extension that is not part of the DSCSA requirement, but the industry has decided it is an important part of the EPCIS file. As such, the EPCIS is more than a compliance document; it is actually a trade document that has a component used for compliance.

Labeling Harmonization

Labeling inconsistencies are also problematic. When using different contract packagers for the same product, care should be taken to harmonize labels. This avoids confusion for the receiver, who may assume the product is illegitimate or counterfeit. Similar problems can arise if the print quality of the labels degrades to the point for which the barcode cannot be read. Receivers may surmise that those products are mislabeled. Products end up getting returned or, in some cases, reported as illegitimate.

All factors involved in every process should be considered when reviewing procedures and their optimization. The various guidance documents are extremely useful references for this undertaking.

MANAGING PROBLEMS

It is inevitable for issues to arise, even after careful planning. Anticipating potential problems and developing strategies for their amelioration can make the difference between experiencing a minor hiccup and losing a major customer (see **FIGURE 3**).

FIGURE 3: What to do when issues arise, even after careful planning.

- Backup and recovery. Are you sure?
- Alternate processing if primary fails.
- Warehouse errors, such as cycle count or damage.
- Suspect products are reported by your buyer.
- Correcting transaction documents (TD) with errors.
- Are Standard Operating Procedure (SOP) and work instructions (WI) adequate, and will pass inspections?

Backup and Recovery

Many assumptions are made regarding backup and recovery. A dry run should be performed to ensure the system can actually be recovered. Some companies use cloud-based services and simply assume everything is fully backed up and recoverable, only to later find that a discrepancy has crept into the system. Suddenly, something that was never a problem before starts to manifest into day-to-day operations. It then becomes necessary to recover a backup or revert to a previous stable, validated version. A process should be in place for that scenario to address this mission-critical issue. Failure to do so could result in delays in the ability to ship products, which, for many businesses, would impact their reputation. It may also cause buyers to look at alternative suppliers and may lead to the loss of orders and business.

In one case, a minor change to a firewall that was thought to be inconsequential ended up becoming a two-week outage because no one could determine why the AS2 connection failed to deliver the data properly. This is an example of a little variable that can go uncounted during implementation only to ultimately cause the business extreme, unexpected turmoil. To minimize process interruptions, backup and recovery should be thoroughly reviewed and tested.

In that same vein, alternative processes should be in place to handle emergencies with interfaces and edge systems. If those systems fail, the normal handling of serialized products may be impacted and could stop operations such as shipping products to buyers. A fallback position should be ready, similar to a spare tire for a car. The tire is not intended to be used forever, but during an emergency it can transport someone to a place where they can get service. Likewise, companies should develop alternatives to their primary process for managing crises, and they should be wrapped into the validation process along with the primary systems. Failure to validate the backup processes can result in unexpected trade issues when they are in use.

Warehouse Errors and Damaged Product

Warehouse errors, such as those relating to cycle count or damage, must be accounted for and reconciled. Although recording the serialization is not required unless the product is shipped, most companies maintain some type of a reconciliation. In the event of a low cycle count, companies need to determine what products are missing and where they went. This understanding is necessary in case they show up in an investigation. A high cycle count triggers an investigation into how the products were obtained and from where they came. It may also indicate other problems that were previously unrecognized.

If damaged product is found, the serial numbers should be captured, if possible, so they can be decommissioned from the system to prevent their shipment. This also helps investigators determine what may have caused the damage.

Anticipating potential problems and developing strategies for their amelioration can make the difference between experiencing a minor hiccup and losing a major customer.

Suspect Products

Suspect products reported by the buyer must be taken very seriously. The reports are time sensitive and have the potential to trigger a full-blown investigation. The need to have a robust, detailed process for handling those products and getting back to the buyer about the investigation cannot be overstated. Adequate information should be collected from the buyer who is holding those products and is unable to distribute them. It should not be taken lightly that the buyer is waiting to hear back before they can do anything with the product.

Transaction Documents

Correcting errors in transaction documents is also critical. For example, if a company provides a transaction document stating 10 products were sent but only nine were actually shipped or lost in transit, the receiver will expect a corrected document that reflects the discrepancy in a timely manner. This allows them to avoid DSCSA compliance responsibility for the unreceived product. Thus, a well-planned process for handling and adjusting transaction documents should be established.

Standard Operating Procedures and Work Instructions

Standard Operating Procedures (SOPs) and work instructions (WI) are undergoing greater scrutiny now, so they must be fully complete and able to pass inspections. Processes should be in place for all anticipated problems to help defend against surprises. A common mistake is isolating serialization corrections from other actions to correct an issue. An example is a shipping quantity error, where billing and related documents, and serialization must be corrected. This adds risk if the serialization correction is overlooked. Instead, many companies have begun to integrate serialization actions into existing procedural documents to avoid mistakes.

EVALUATING READINESS

All processes and business relationships should be examined to determine their state of readiness for DSCSA compliance (see **FIGURE 4**). While many companies believe they are well prepared, some of their procedures and partners along the supply chain are not.

Suppliers

Because the FDA has granted a one-year stabilization period during which they are not issuing fines for noncompliance with DSCSA, some companies are not yet providing the required DSCSA information. This means that companies doing business with them, as well as those further down the supply chain, are unable to comply with the new law. Dispensers, for instance, cannot retain serialization as required by the law if it is not provided by the supplier. Thus, they must request a waiver from those suppliers to protect themselves from potential repercussions.

FIGURE 4: Evaluating readiness for DSCSA compliance.

- Suppliers?
- Labeling?
- Buyers?
  - Drop shipments.
  - Dispensers without EPCIS support.
- Verification.
- Returned (including cancelled shipments).
- Procedure gaps for DSCSA compliance.

Buyers

Similarly, buyers must be ready to receive the information from suppliers. When they are not, many companies record the shipping details and serialization, so the information is retained. To be compliant, portal access can be set up to provide an electronic copy of the information without needing the buyer to receive it through a standard format, like EPCIS.

Labeling

Labels should be scrutinized for inconsistencies and labeling processes well documented, with controls in place. It is extremely common for labels to have unforeseen issues. For this reason, an independent review is strongly recommended, such as by a logistics partner or 3PL. Processes should be developed for inbound inspection and reports regarding anything that might become an issue downstream.

Procedures should also be established for drop shipments, even if they are not currently performed. They may arise later and there are subtleties to setting up drop shipments to comply with the requirements of DSCSA. SOPs are necessary for dealing with dispensers who use a portal instead of EPCIS.

Verification

Regarding verification, some companies believe they are prepared but the system has never actually been used. The verification router service (VRS) system must be checked for readiness, as there is information that must be added to the product master for the VRS to function.

Returned and Cancelled Shipments

Readiness for returns and cancelled shipments must be fully evaluated. As mentioned previously, detailed procedures are necessary for consistent management of these cases.

Procedure Gaps for DSCSA Compliance

It is advisable to look for procedural gaps in DSCSA compliance. Companies should examine current policies and procedures and identify gaps in readiness. This includes assessing procedures to ensure they are detailed enough so someone could determine that they are repeatable and can be consistently executed.

ALTERNATIVES AND EMERGING TRENDS

Third-party logistics (3PL) service providers can assist companies with DSCSA compliance by assuming some or all required activities. They may host the system; leverage technology, such as Amazon web services; and offer other distribution services. Several 3PLs supply serialization, including direct shipment to buyers. Of note, several will handle the serialization but won't directly interact with the buyer. This leaves the company exposed, as they must receive the details of the shipment from the 3PL and then forward those details to the buyers themselves. To eliminate this extra step, more and more 3PLs send the information directly on the company's behalf. It should be noted that there are differentiators in terms of the degree that 3PLs comply and their processes. If a 3PL offers the service, companies should closely examine what assistance they are offering and how that compares to other providers. A 3PL vendor is really a collection of services such that all the different functionalities should be evaluated, and DSCSA compliance or serialization handling are not all the same or a single checkbox when comparing 3PL providers.

Some 3PLs offer comprehensive serialization services so that a company would not need their own serialization system; they merely leverage the 3PL's serialization systems and DSCSA compliance offerings. The service provider simply receives the serial numbers from the packager, retains the serial numbers, picks, packs, and ships the products, and sends the DSCSA compliance information to the buyer. They often manage other aspects of DSCSA compliance, such as suspect product investigations and orders, including verifying the buyer as a licensed and authorized distributor record. Overall, they offer a more robust offerings, so a business does not have to concern itself with managing the serialization. Very few companies, if any, run the serialization themselves; they pay a service provider to do that. So, a 3PL offering full serialization is similar but avoids two separate service providers or issues associated with interfacing a serialization provider with your 3PL.

The industry is seeing an evolution of the portals that are offered for serialization information. Many of the early portals required companies to use an interface with the serialization provider's operating system. However, buyers may be unfamiliar with that system and need separate training for each of the portals for the various products they purchase from separate brand owners. In fact, different systems are available via different companies, and their operation and features are very different. Because each portal may be different, special training may be necessary. The systems have limited functionality and most of the portals are designed to deliver an EPCIS file that many of the smaller buyers at the end of the supply chain do not want.

If a 3PL offers the service, companies should closely examine what assistance they are offering and how that compares to other providers.

To address this, some companies offer a very focused portal just for dispensers and small businesses at the end of the supply chain, providing human readable forms, with very intuitive, zero training interfaces. These types of portals provide companies with the ability to confirm a serial number and review all transaction information, as well as the parent-to-child serialization information, all in a simple human readable form.

Convenient kits are also available for maintaining DSCSA compliance. As providers kit the products, they expect companies to do their own serialization and provide the labels, etc. However, some of the providers of the kitting services, especially some of the 3PLs, will provide the labeling, aggregation, and more, to finish it out so the kit is fully DSCSA compliant. If it has multiple drugs in it, they will aggregate the serial numbers of those different drugs against a parent serial number on the kit. Thus, the kit itself has aggregation that allows for traceability of the serialization all the way down into the kit.

Some manufactures are seeking to sell their products in the United States. Adding the required labeling, collecting child-to-parent aggregation, and managing the serialization can be a barrier to entry. Some 3PLs provide labeling, aggregation, and serialization management to facilitate entry. When coupled with other services, such as flash title, for which the 3PL assumes the ownership before shipment and leverages their licenses for distribution, some 3PLs offer a favorable choice for quickly entering the US market.

Another emerging trend is applying serialization to samples, clinical trials, and medical devices. Since companies are establishing serialization systems anyway, the same serialization can be extended to the sampling business, clinical trials, and even to medical devices. As that information is collected, it can be used for different business reasons. This includes delivering improved exposure to where samples end up and what type of trade those samples might potentially go through. Moreover, serialization can provide a unique way of identifying particular patient trial materials for a clinical trial. Some very extensive blinding can be performed as well, by recording groups of serial numbers for a placebo comparator or the actual trial. Medical devices can easily be tracked by recording information in the same system that is already being used for pharmaceutical products. The application of serialization beyond DSCSA requirements is expected to grow as more opportunities are recognized.

CONCLUSION

Implementation of requirements to meet the FDA's DSCSA can be very complex and confusing. It is not uncommon for surprises to occur, even after a company believes they are in full compliance. To ensure readiness, judicious planning is warranted, including developing detailed processes to handle all aspects of operations. Additionally, engaging independent reviewers to evaluate processes and demonstrate they are repeatable and can be consistently executed is advantageous.

Third-party logistics (3PL) service providers can simplify the compliance journey for companies by taking on the burden of serialization, labeling, aggregation, verification, orders, shipments, returns, suspect product investigations, and more. As the functions offered by some 3PLs can vary, the selection of service provider within the purview of DSCSA compliance should involve thorough consideration.

The concept of serialization can be widely employed, making it amenable to many other business and research functions. For example, it is emerging as a valuable asset for tracking samples, clinical trials, and medical devices. Although setting up serialization can be complex, the information it provides for any application is enormously beneficial.