

Introduction

DSCSA (Drug Supply Chain Security Act, Pub. Law No. 113-54, 127 Stat 599 (2013)) has been enacted to address the vulnerabilities of the pharmaceutical supply chain and to strengthen the security of drug distribution within the supply chain. Some of its goals include improving patient safety and the efficiency of recalls and reducing counterfeit products. Both recalls and counterfeit products impact patient safety and have the potential to cause death to the consumer. While we appreciate the steps taken to make the supply chain more robust, we are worried about some of the more critical aspects that might increase but do not contribute to the goal of improving patient safety, the efficiency of recalls, and reducing counterfeit products.

Main Challenges:

Product Quality and Authenticity - Diversion and Counterfeiting

One of the important goals of DSCSA is to reduce counterfeit medication and diversion within the supply chain. These are defined as follows:

- A counterfeit drug is a medication or pharmaceutical product that is produced and sold with the intent to deceptively represent its origin, authenticity, or effectiveness.
- Product diversion is a means for counterfeiters to access the product, to insert fraudulent goods into the system, which ultimately results in revenue loss.

Diversion and counterfeiting are nefarious, illegal practices that result in tainted or fake medications entering the medical supply chain. These practices can be harmful or deadly when counterfeit medications are dispensed and administered to patients.

A product can be considered a counterfeit for many reasons. Counterfeit products are not of the same quality, formula, or ingredients. Typically, counterfeiters disguise their non-authentic products by reusing authentic packaging, labels, vials, bottles, and syringes. Increased visibility and traceability throughout the entire product life cycle is crucial to significantly reduce diversion and leaks within the supply chain.

The conditions of the drug (temperature, moisture, sunlight, etc.) during its journey within the supply chain can potentially have a detrimental effect on the safety and quality of these medications, many of which must be stored within a predefined temperature range. Lack of positive control can ultimately result in product damage. Given the lack of traceability and real-time visibility while a medication is being shipped, it is difficult to identify if and when a temperature excursion has occurred. Without this data, it is impossible to identify and intercept the product before being delivered to the patient. Spoiled products can be damaged, destroyed, and product concentrations can be impacted making medications, less effective, harmful, and, in some cases, even deadly.

Environmental temperature during transport is not the only factor that leads to product quality and safety issues. For instance, a medication may have a sensitivity to light and air, being shaken, and exposed to vibrations or mishandling. Tampering can result in product dilutions, ingredient additions, and even product substitutions with fakes.

Building an interoperable electronic system can improve tracing but if the technology underneath is not able to detect the counterfeit, the electronic system may not be sufficient. With 2D barcodes for instance, product information can easily be printed and attached to a counterfeit product. Unfortunately, a counterfeit product

disguised as a genuine one, with identical information printed on its barcode would be impossible to detect. As seen in several cases, extra layers of printed information can also be placed over barcodes to tamper with information. For DSCSA to achieve its objectives, a more comprehensive solution is required to ensure counterfeit products are not allowed to enter the supply chain.

To fight the scourge of counterfeiting, the End-to-End (E2E) supply chain must have the ability to verify the authenticity of the products at any point within the supply chain. E2E visibility and direct end-user feedback are essential for traceability. The ability to deliver high-quality, authentic, adequately dispensed medications when and where needed is critical to patient health and should be the goal of the DSCSA.

Manual Errors

In an interoperable system manual errors prove to be costly. Using barcodes alone for traceability requires increased human intervention, which has the potential to result in additional confusion and transmission errors. Common errors may include:

- Scanning an incorrect barcode
- Low contrast between background (unprinted space) and information (printed space)
- Errors while inputting the data manually

The list is not limited to the above, and errors can cause a ripple effect down the value chain. In the case of a complete interoperable system, one manual error can lead to inefficient tracing or product recall, and very costly returns.

Lack of Standardization

While the DSCSA outlines steps for building an electronic, interoperable system to identify and trace certain prescription drugs, the lack of standardization may hurt the pharmaceutical supply chain. The industry might arrive at a solution involving the adoption of an electronic system such as a blockchain platform, or another Enterprise Resource Planning system like SAP, but these electronic systems need a dependent system like barcode or Radio Frequency Identification (RFID) to operate. Lack of standardization on the usage of barcodes for product information will likely create numerous issues. The visibility, legibility, and order of product information, and the usage of the utilization of this data on barcodes should be standardized. With traceability required down to the unit level, all the units command the need of product information in human and machine-readable form which either increases the size of the packaging, or reduction in font size both of which are problematic.

Future, Scale & Automation

A standard barcode does not allow scanning machines to read multiple products at once. Products must be scanned individually to input the data. This substantially slows down the operating speed and increases the labor costs and potential for human error. The concept of scanning each product adds considerable time into the supply chain which leads to increased costs and the potential for errors. To solve this challenge, the industry

should seek to integrate new technologies to supplement barcodes as the underpinning technology for electronic interoperable systems to make the pharmaceutical supply chain robust and tamperproof.

Our Proposed Solution

The ideal End-to-End (E2E) traceable value chain will provide many benefits and will add value to each node of the supply chain. The benefits of an E2E traceable value chain significantly address patient safety, product quality, product authenticity in the pharmaceutical supply chain by reducing diversion and counterfeiting, profitability, and potential drug shortages (*Figure 1*).

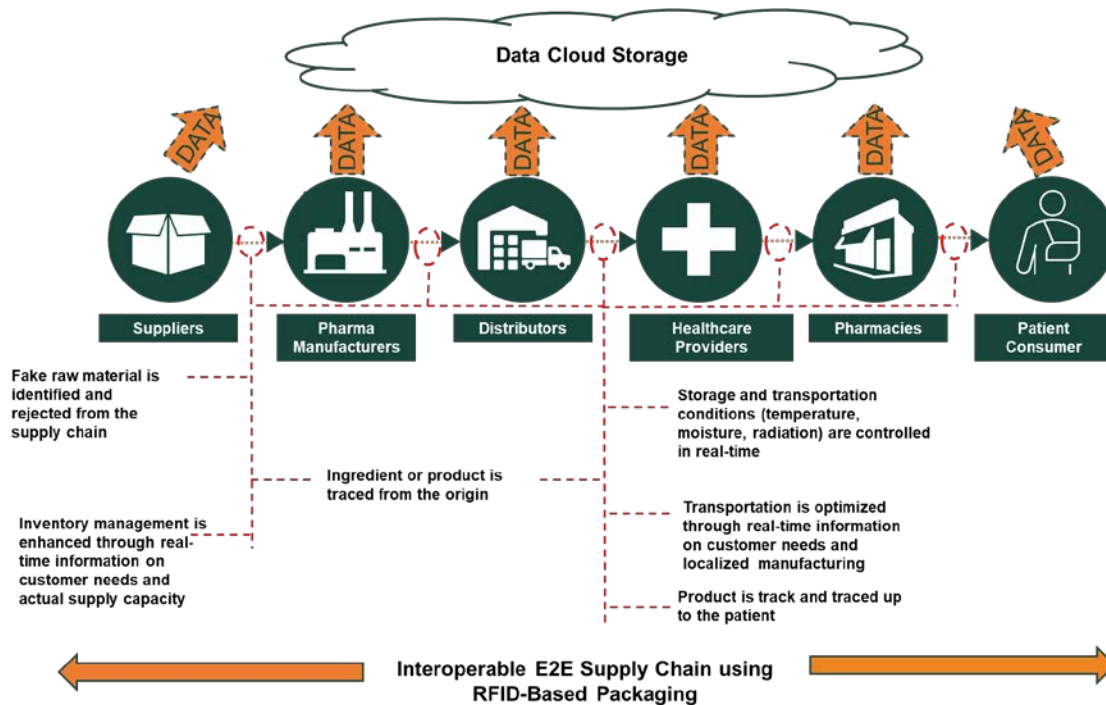


Figure 1. End-to-End Traceable Pharmaceutical Supply Chain and Potential Benefits

With E2E traceability, supply chain members can monitor the progress of the product as it leaves and arrives at the various nodes within the supply chain. They will be able to screen and monitor in real-time when a product is diverted, thereby enabling interception and risk remediation and elimination of counterfeits. Given enhanced visibility and traceability, every node in the supply chain can be confident in the authenticity of the product because they can track the journey of the product.

Importantly, with this traceability it is possible to detect products that did not originate from the manufacturer, are diverted during transport, that enter the supply chain at the incorrect time or location or reenter the supply chain after they were previously distributed. This new detection service would trigger alerts that a product may have been diverted, counterfeited, or otherwise tampered with during transportation and storage. If additional data provided by smart sensing and packaging indicates the quality of the product has been compromised and is no longer of intended quality or safety, a member of the supply chain would be able to intercept this damaged product before it is administered to the patient.

To provide E2E traceability and ensure that patients receive authentic medications, dispensers must be able to trace the individual product back to the originating manufacturer. For this to occur, the dispenser should have the ability to track back along the supply chain to confirm any product's authenticity. Enabling this system requires capturing this data stream and making it visible to dispensers and patients so that they can have confidence in the effectiveness and quality of the medication. Many emerging technologies are now available to bring E2E traceable solutions to the medical industry, and many are in use in other industries. For instance, the Internet of Packaging (IoP) is the application of the Internet of Things (IoT) into packaging and could provide necessary visibility and traceability. IoT is a complex network of physical and non-physical components in which electronic information (data) can be produced through different devices and shared over a network of components. Wireless sensor networks, Near Field Communication (NFC), and UHF RFID technology are known as the major components of IoT. Similarly, IoP includes emerging physical, electrical, and detection technologies integrated into packaging that combines with data analytics to monitor the condition of the material inside the package and its surrounding environment. The collection of these data in real-time ensures authenticity and product quality.

RFID tagged at the source by the manufacturer will address illegitimate products, manual errors, operating scale, and standardization issues. RFID can create a tamperproof mechanism for tracking medications across the supply chain as its usage makes the counterfeiting of drugs next to impossible. Because many products can be read at the same time, the operating scale and automation errors caused by manual barcode scanning would not be present. The perception is that bar codes are “free” and RFID tags are expensive. However, the cost of RFID can be justified when comparing the limitation of exclusively using barcodes related to the cost of counterfeit medications, misreads, work arounds, and human errors with the speed and accuracy of RFID. Also, the cost of RFID has come down while performance has increased. With a wide adoption the costs will continue to drop.

In summary, the FDA should consider recommending RFID technology instead of barcodes to meet its goals as it provides a significantly better solution for managing medications across the pharmaceutical supply chain.

Case Study – Fresenius Kabi

Fresenius Kabi, a global healthcare company, launched an ambitious program to support healthcare providers and become the first in its industry to tag vials of medication using Electronic Product Code-enabled Radio Frequency Identification (EPC/RFID) technology (<https://www.plusrfid.com/>).

Fresenius Kabi chose an EPC/RFID tagging system based on GS1 Standards which enable any supply chain participant across the globe to read data with the proper RFID equipment, including hospitals and pharmacies that comprise Fresenius Kabi’s primary customer base. By tagging each dose of medication, the healthcare provider and patient have an additional serialized measure of unique product identification.

Cross-Collaboration

It is considered practically impossible to completely isolate the different parts of a product supply chain to immunize it against counterfeiting, tampering, and contamination. Thus, there is a need for end-to-end trust

verification for the entire value chain to enhance patient safety, patient health, product quality, and product authenticity by reducing diversion, counterfeiting, profitability, and potential drug shortages.

A cross-collaboration between RFID Tag Manufacturers, Pharmaceutical Manufacturers, Medication Automation, and Healthcare Technology Providers, and Verification Entity (Axia Institute) is needed to design, implement, and verify the EPC/RFID tagging system based on GS1 Standards.

The Axia Institute acts as a neutral third-party to verify the properties of RFID-tagged items based on the requirements of GS1 using Tagged-Item Performance Protocols (TIPP) guidelines (<https://axia.msu.edu/>). TIPP guidelines effectively simplify communication of tagging performance requirements among stakeholders (Figure 2):

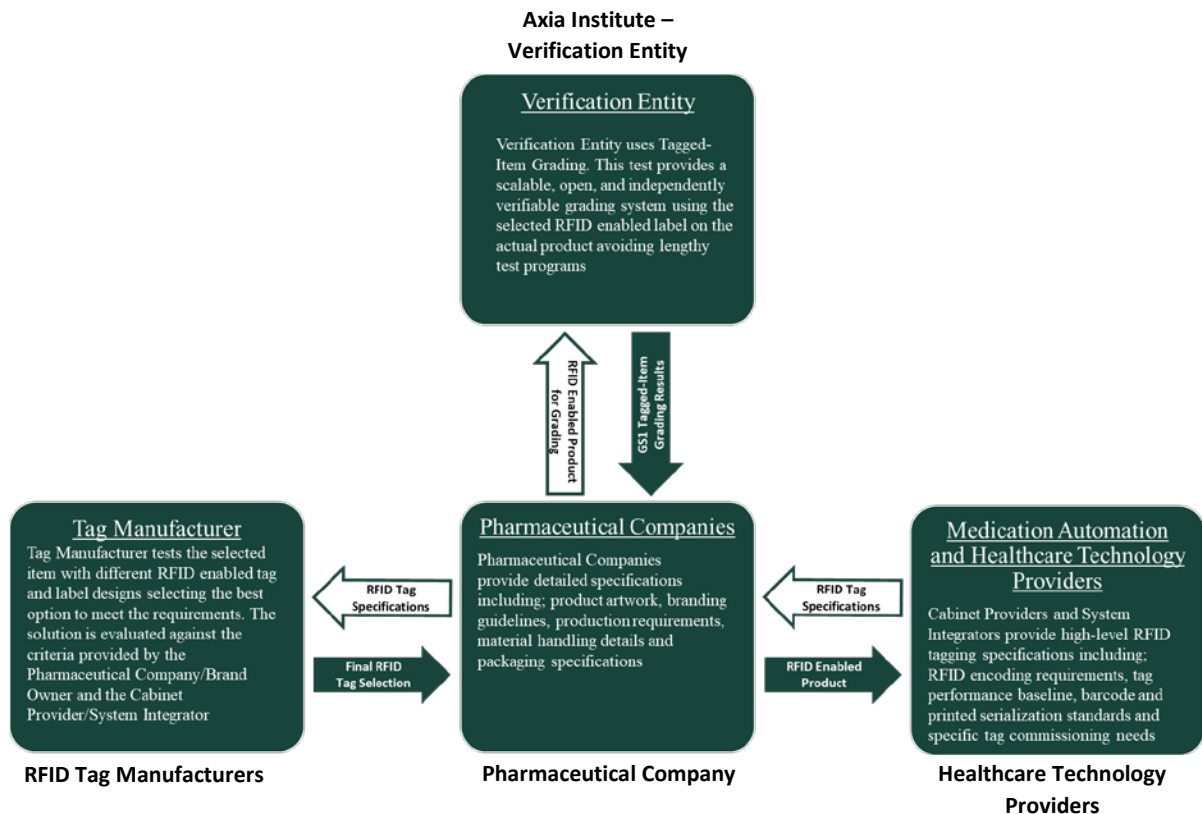


Figure 2. Cross-collaboration to design, implement and verify the EPC/RFID tagging system based on GS1 Standards.

- Medication automation and healthcare technology providers (including automated dispensing cabinets, EHR providers, medication dispensing robots, IV workflow technology, central pharmacy automation, pneumatic tube systems and smart cabinets) can specify tagging requirements in TIPP grades, and therefore help the manufacturers to supply tagged products that can be reliably inventoried.
- Pharmaceutical companies communicate requirements through TIPP grades to Tag Manufacturers and Reader Suppliers.
- Pharmaceutical companies, RFID technology providers, and medication automation and healthcare technology providers work together to optimize tagged item specifications and tagged item reading events.
- Shared terminology and clear acceptance criteria lead to less complexity, less management and is more efficient for high volume overall system design.

Anticipated Benefits

- Hospitals that are applying their RFID tags to pharmaceuticals no longer need to expend time-consuming effort (and avoid potential process-quality or security issues) when using drugs from manufacturers that supply their products with RFID tags embedded in the label of each dose.
- Supplying the combination of the GTIN, serial number, and tag ID, the RFID-tagged drug is virtually impossible to counterfeit, strengthening serialization already in place in compliance with the U.S. Food and Drug Administration (FDA) Drug Supply Chain Security Act (DSCSA)
- In the event of a recall, the identity of targeted items can be pinpointed, with the item date, batch/lot, serial number, or other related manufacturing details.
- Hospitals can achieve more precise inventory management with the ability to read many RFID tags simultaneously. This could lead to better drug management overall, and improved charge capture in hospital settings where barcode scanning is not conducive to the workflow.
- Standard protocols and guidelines can be developed and verified to efficiently implement the combination of the GTIN, serial number and tag ID, and RFID across an E2E supply chain.

Conclusion

The DSCSA goal of tracing medications in the pharmaceutical supply chain is critical for ensuring patient safety. The complexity of the medical supply chain is such that there are many vulnerabilities that can be taken advantage of by dishonest parties seeking to steal legitimate product while injecting counterfeits into the system. Today's de facto standard barcode labeling processes are prone to errors (human or otherwise) as well as tampering risk. These shortcomings further inhibit the industry from reaching its goal of achieving traceability in the supply chain. Above all, they support the need for a more robust, multi-layered system of securing the flow of medications across the medical value chain.

The Axia Institute encourages the FDA to endorse item-level RFID tagging in addition to barcoding technology because together they provide a clearer path to traceability for all medications across the supply chain. Importantly, it also provides all members of this value chain with the opportunity to contribute to the FDA's stated goal of improving patient safety and the efficiency of recalls and reducing counterfeit products in the medication supply chain.