# **Falsified Medicines and Drug Supply Chain Security**

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**Abstract**

On January 1, 2015 the United states Drug Quality and Security Act (DQSA) went into effect. Part I of this Act is about Drug Compounding and Part II is about Drug Supply Chain Security (DSCS). The Act established national standards for prescription drug distribution supply chain practices to track and trace product from manufacturer through wholesalers and distributors to dispensers and back for returns. Compliance to these new standards is not optional and requires specific computerized transaction history records to be generated and kept for at least six years. .

**Key Words:** Lot serialization, drug distribution security, drug supply chain, drug track and trace system

## **INTRODUCTION**

The global distribution process for prescription drug products is very complex and filled with multiple layers of third party and outsourced components. There are contract manufacturing organizations (CMOs), wholesalers, distributors, dispensers, and logistics contractors and vendors across the globe. Over the years, industry has experienced problems with counterfeit product, adulterated product, and mishandled product resulting in consumer injury, loss of market share, and loss of profit.

With no established global business or regulatory standards in place to counteract such issues, industry has had an ever increasing challenge to fight back on a company by company basis. Now various regulatory authorities are coming forward with standards and guidance such as the 2011 European Falsified Medicines Directive 2011/62/EC and the United States Drug Quality and Security Act established in 2013 with initial phase terms effective as of January 1, 2015.

## **Auditable Chain of Custody**

Both the EU Directive and the US FDA Act stress the need for electronic means to **track** specific product items from manufacturer through the distribution process to dispensers, e.g. hospital and commercial pharmacies. Both also stress the need to be able to **trace** returned or questionable product back through the chain from dispenser to the manufacturer. Thus the terms Track-and-Trace data and Track-and-Trace systems are being used to characterize the hardware, software, and databases employed for this purpose.

An auditable Chain of Custody requires the formal logging of product movement through the distribution path. Who is doing what with the product, where, when, why, and how? Then required approvals and sign-offs as per standard operating procedure (SOP). Is someone a wholesaler, a repackager, a redistributor in another country, a transport or logistics shipping vendor? A variety of roles and responsibilities are involved.

By 2018, the EC Directive looks to have a Stakeholders’ Repository established. This will be a protected centralized database managed by stakeholders and supervised by EU authorities with End-to-End scanning process and verifications by wholesale distributors. Manufacturers will use a 2D barcode (data matrix) set as carrier of a product Unique Identifier (UI). The EC Directive specifies the UI required content to be Manufacturer’s product code; serial number; national reimbursement number, if present; batch number; and expiry date. (2)

The US Food and Drug Administration (FDA) aims to improve the traceability of prescription drugs within the supply chain over a ten year period 2013-2023 implemented in three major phases. (1)

* Phase 1: Lot-level traceability and verification by January 1, 2015 for manufacturers, wholesalers, and repackagers.
* Phase 2: Unique serialization. From 2017-2019, single packages of drug products have to be marked with serialization numbers and bar codes.
* Phase 3: Serialized Item-level traceability. From 2023, information must be provided to allow supply chain partners to trace transaction history back to initial manufacturer or repackager.

## **FDA Key Terms and Concepts**

In February 2011, the FDA held a workshop to join with industry and other stakeholder parties to explore and examine track and trace options and their respective impact on consumers, business practices, and profits. A number of key terms were defined and described for the workshop to establish a common vocabulary that would facilitate clarity in group discussions. (3) They included the following:

| FDA Term or Concept | 2011 FDA Workshop Definition |
| --- | --- |
| Serialization | Process of uniquely identifying a product. FDA issues recommendations in the Standard Numerical Identifier (SNI) Guidance. March 2010 |
| Drug Package | The smallest unit placed into interstate commerce by manufacturer or repackager that is intended for individual sale to the pharmacy or other dispenser of the drug product. |
| Standardized Numerical Identification (SNI) | SNI components include:   * Serialized National drug Code (sNDC) * NDA 55555 666 77 ( labeler code + product code + package code) * + Serial Number 11111111111111111111 (unique, up to 20 characters) |
| Interoperability | Compatible data and process standards to allow data sharing by integrating into the same system. |
| Authentication | Verifying that the Standardized Numerical Identification (SNI) on a prescription drug package is a valid number and confirm there are no discrepancies in the distribution history. |
| Track-and-trace data | Any information collected about each package from the point of manufacture to the point of dispense or destruction. |
| Pedigree | Distribution history of a drug package. |
| Status | Description of package distribution as it moves through the supply chain (e.f. recall in process, in transit, destroyed, dispense, stolen, etc.) |
| Data management | Provides standardized mechanisms that supply chain participants use to capture, store, protect and utilize track-and-trace data to facilitate authentication and interoperability. |
| Accountability | When a person or entity has to report, explain, justify, or be responsible for, or effectively takes custody or ownership of a package. |
| Counterfeit drug | A drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, to have been packed or distributed by such other drug manufacturer, processor, packer, or distributor. (FFDC Act) |
| Drug Supply Chain | Manufacturers & Contract Manufacturers  Primary Distributor(s)  Repackager(s)  Secondary Distributor(s)  Pharmacies |
| Ref: FDA Workshop Feb. 15-16, 2011 (3) | |

## **Track-and-Trace System Goals and Attributes**

The globalization of supply chains has added many complex dimensions to the pharmaceutical product distribution logistics. Rules vary by country and state. Criminal activities such as diversion, cargo theft, and counterfeiting can occur anywhere along the chain to pharmacies. Goods are stolen and reintroduced into the supply chain. Counterfeit goods are sold to suppliers and re-enter the supply chain. The 2011 FDA Workshop presented their goals for a Track-and-Trace system to be –

* Prevent the introduction of counterfeit, diverted, sub-potent, substandard, adulterated, misbranded, or expired drugs.
* Facilitate identification of counterfeit, diverted, sub-potent, substandard, adulterated, misbranded, or expired drugs.
* Provide accountability for the movement of drugs by supply chain participants.
* Improve efficiency and effectiveness of recalls.

To achieve such goals, a Track-and-Trace system must have certain attributes that enable it to fulfill the following FDA requirements:

1. Be able to capture unique product identification and status of the number.
2. Ensure interoperability to enable supply chain participants to securely capture, store, and exchange track-and-trace data accurately and efficiently.
3. Authenticate the SNI and entire distribution history of each package.
4. Enable appropriate access to track-and-trace data necessary to achieve system goals.
5. Ensure security of data and systems from falsification, malicious attacks, and breaches.
6. Ensure confidential commercial information is protected
7. Ensure patient privacy is maintained, if applicable.

## **FDA Drug Quality and Security Act Title II: Drug Supply Chain Security Act (DSCSA) of 2013**

The final outcome of the 2011 FDA workshop was the FDA’s two part regulation Drug Quality and Security Act in 2013. Title I of this Act is on Drug Compounding. Title II is on Drug Supply Chain Security with a focus on track-and-trace of each transaction link in the chain from manufacturer to dispenser. Title II section 581(24) defines the term “transaction” to mean “the transfer of product between persons in which a change of ownership occurs.” Title II section 581(25) defines “transaction history” to mean “a statement in paper or electronic form, including the transaction information for each prior transaction going back to the manufacturer of the product.”(1)

DSCSA is very specific in describing just what transaction information should go into the Transaction History document. Title II section 581(26)

1. The proprietary or established name or names of the product,
2. The strength and dosage form of the product.
3. The National Drug Code number of the product.
4. The container size.
5. The number of containers.
6. The lot number of the product.
7. The date of the transaction.
8. The date of the shipment, if more than 24 hours after the date of the transaction.
9. The business name and address of person from whom ownership is being transferred.
10. The business name and address of person to whom ownership is being transferred.

In addition a Transaction Statement is required to verify that the conditions of the transaction are valid. The DSCSA describes a Transaction Statement as a statement, in paper or electronic form, that the entity transferring ownership in a transaction – Title II section 581(27)

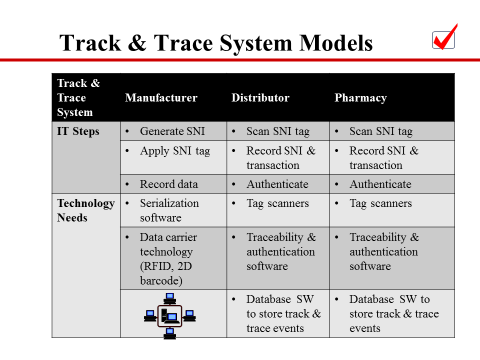
1. Is authorized as required under the Drug Supply Chain Security Act.
2. Received the product from a person that is authorized as required under the Drug Supply Chain Security Act.
3. Received transaction information and transaction statement from the prior owner of the product, as required under section 582.
4. Did not knowingly ship a suspect or illegitimate product.
5. Had systems and processes in place to comply with verification requirements under section 582.
6. Did not knowingly provide false transaction information, and
7. Did not knowingly alter the transaction history.

The DSCSA goes on to state implementation requirements for manufacturers. Beginning not later than January 1, 2015, a manufacturer shall – Title II section 582(b,1,A)

1. Prior to, or at the time of, each transaction in which such manufacturer transfers ownership of a product, provide the subsequent owner with transaction history, transaction information, and a transaction statement, in a single document in a paper or electronic format; and
2. Capture the transaction information (including lot level information), transaction history, and transaction statement for each transaction and maintain such information, history, and statement for not less than six years after the date of the transaction.

## **Track-and-Trace System Planning and Regulatory Compliance**

The technology needed to provide track and trace capability to industry was described at the model level in the chart below used at the February 15-16, 2011 FDA Workshop. (3)



The manufacturer uses serialization software and data carrier technology to fully label the product item and generates a Standardized Numerical Identification (SNI) tag as the foundation of the product history and verification process. The rest of the chain members use tag scanners, traceability and authentication software to verify the product’s transaction history and statement. A centralized database is then used to store the full chain of Track and Trace records.

Track-and-Trace data is subject to regulatory review and copies/reports of transaction and recall information must be provided when requested from FDA, EMA, and various other national authorities. The computerized systems used in this chain of procedures are expected to comply with 21 CFR Part 11 (FDA) and EU GMP Annex 11 (EMA) quality standards. Both regulations require documented evidence of validation, formal testing, user training, and standard operating procedures (SOPs) for such systems.

## **GAMP Template for Track-and-Trace Central Archive Systems**

In mid-2015, much of the Track-and-Trace software, network and business logistics, and specific systems technologies continue to be in ongoing development. This is a huge undertaking for the drug industry and its many global suppliers and most companies are in a struggle to meet regulatory expectations for Track-and-Trace. The Good Automated Manufacturing Practice (GAMP) Guidance for Electronic Data Archiving (ISPE 2007) can provide strong support for planning and implementing the centralized Track-and-Trace internal, central archive database for the Track-and-Trace records of a company’s prescription products.(4)

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