White Paper

Security of Pharmaceuticals

Comparing US and EU Standards

What have the Falsified Medicine Directive (FMD) and the Drug Supply Chain Security Act (DSCSA) in common and what are their differences? This white paper presents the main provisions of both legal frameworks and thus assists in developing a deeper understanding of the requirements for pharmaceutical companies.

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METTLER TOLEDO

1 Introduction

Europe and the United States are considered the world leaders in the safest pharmaceutical markets for patients. However: With 840 million inhabitants, and two-thirds of global pharmaceutical sales, the US and Europe are also a lucrative target for drug crime. New sales channels such as the internet as well as global and more complex manufacturing and distribution channels make it increasingly easier for pharmaceutical counterfeiters to market counterfeits directly or to infiltrate the supply chain. Thus, in the annual "Operation Pangea", an international week of action for combating the trafficking of illegal drugs on the internet coordinated by Interpol, more than 50,000 websites were shut down in the years 2011 to 2016 alone.

With the EU's counterfeit protection directive 2011/62 / EU Falsified Medicine Directive, (FMD) and the Drug Supply Chain Security Act (DSCSA), the European Union and the United States have adopted a comprehensive legal framework for greater patient protection and set the stage for even greater pharmaceutical security.

This paper describes the essential regulations in both legal frameworks and the resulting requirements for pharmaceutical companies.

2 Legislation in the European Union and the US

2.1 Counterfeit Protection Directive 2011/62/EU

On 8 June 2011 the European Parliament and Council adopted Directive 2011/62 / EU (counterfeit protection directive) amending Directive 2011/83 / EC establishing the Community code relating to drugs for human use. With the release of the Delegated Regulation (EU) 2016/161 on 9 February 2016, the legislative process has been completed and its defined implementation dates are now in force.

From 9 February 2019* only those prescription drugs which have a unique serial number on the pack and where the integrity of the pack** can be seen may be marketed in all EU countries.

2.2 Drug Supply Chain Security Act

On 27 November 2013 the Drug Quality and Security Act (DQSA) came into force (H.R. 3204). The Drug Supply Chain Security Act (DSCSA) which is Title II of the DQSA, names the compulsory steps on the way to the implementation of an electronic, interoperable system that allows the identification and tracking of marketed prescription drugs in the US.

By 2023, the DSCSA will be well on the way to enabling serialized traceability of individual packages of drugs throughout the supply chain.

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* Belgium, Greece and Italy had already implemented systems for testing the authenticity of drugs before the entry into force of EU Directive 2011/62 and may make use of an extended transition period to February 2025. It is anticipated that only Italy will use a prolonged transition period (as at: August 2016).

** For more information about Tamper Evident procedures and the EN 16679 standard (Packaging. Tamper verification features for drugs packaging), see the METTLER TOLEDO White Paper "Pharmaceutical Tamper-Evident packaging - are you prepared?

3 The FMD and the DSCSA Compared

Both the EU counterfeit protection directive and Drug Supply Chain Security Act have as their core objective the protection of patients from counterfeit and illegally distributed prescription and drugs susceptible to forgery*. Both legislative regulations base this on the serialization of drugs at the level of the sales packaging and other measures to prevent the entry of counterfeits into the legal supply chain. However, the FMD and the DSCSA differ in their conceptual approach - with effects on their respective technical and operational implementation.

The aim of the FMD is to ensure the identification and authenticity of a drug by an **end-to-end checking system** with the use of security features.

Pharmaceutical manufacturers provide the packaging with the two mandatory security features - **a unique identifier** and **a device for tamper protection** - at the beginning of the supply chain.

At the **time of the drug's being dispensed** to the public **checking** takes place to verify the authenticity and integrity of the **security features**.

The verification of the authenticity of the unique identifier ensures that the drug comes from a legitimate producer and has not yet been placed on the market with this unique identifier. The integrity of the anti-tamper device shows that the packaging has not been opened or changed along the supply chain.

The FMD has no documentation requirements for individual transactions along the supply chain.

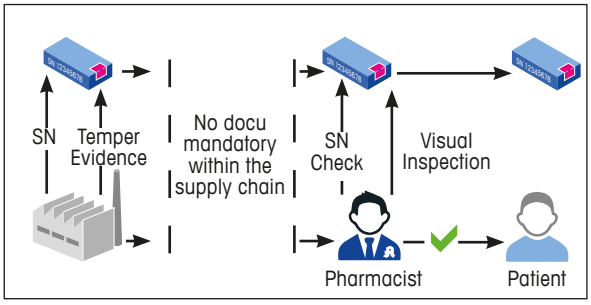
The aim of the DSCSA is to improve **traceability** throughout the US supply chain. Potentially dangerous products should be more easily recognized and identified and recalls in the case of defective products can be performed more efficiently.

The DSCSA addresses every step in the **supply chain** and tracks all stages on the way from the pharmaceutical manufacturer to the pharmacist. Full traceability is provided down to the level of the product's sales packaging for this implementation through to 27 November 2023.

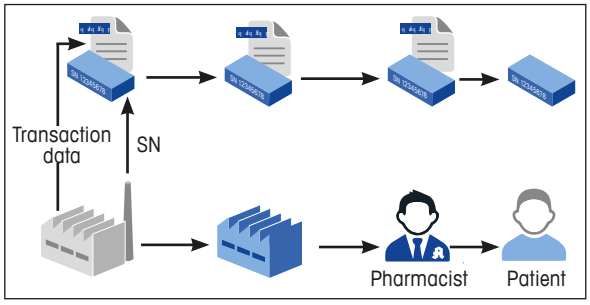
For prescription drugs the **supply chain** extends from the pharmaceutical manufacturer to the doctor **only through authorized trading partners** who are licensed or registered with a state or federal authority.

Electronic data exchange provides the **transaction data for each purchase/sale**. **Verification of the product** takes place at the pack level.

The model does not address the pharmacist verifying the serial number when dispensing the drug.



EU-Model: End-to-end verification system by means of a unique identifier plus tamper protection. Mandatory examination of both security features when the drug is dispensed.



US-Model: Product verification plus documentation of buying and selling along the supply chain. No verification of serial numbers when the drug is dispensed to the patient.

* This was how the first, and so far the only, prescription-free OTC preparation of the acid inhibitor omeprazole in 20 mg and 40 mg capsules was placed on the blacklist of drugs particularly vulnerable to tampering during the implementation of the FMD.

3.1 Legal Obligations for Participants in the EU Supply Chain

Manufacturer	**From 9 February 2019** Serialize the outer packaging, or primary packaging if none exists, of the drug and attach the anti-tamper protection device.
Repacker	**From 9 February 2019** On acquisition, replace the existing drug security features with equivalent security features.
Distributors	**From 9 February 2019** Check the authenticity of the unique identifier (Data Matrix code) for product returns. A test is not necessary when the drug remains in the physical possession of the same distributor or is transferred without a sale between the premises of the distributor or the same legal entity. Check and deactivate the unique identifier (Data Matrix code) when: distributing outside the EU, conducting official tests, removing product from the sales inventory, destruction and, when required by a Member State, for deliveries to consumers to take account of the particular characteristics of the supply chain in its territory. Review certain drugs which are at a higher risk of being counterfeited. This includes returns and drugs not marketed directly by manufacturers, holders of marketing authorizations for distribution or individuals acting on their behalf. Verify the security features when forgery or tampering is suspected. The competent authorities must be notified immediately.
Pharmacist	**From 9 February 2019** Verify the security features at the time when the drug is dispensed and disable the unique identifier (Data Matrix code). Inform the competent authorities promptly if forgery or tampering with the drug packaging is suspected.
Healthcare Facilities	**From 9 February 2019** Review and deactivate the unique identifier at any time at which the drug is in the physical possession of the facility (Prerequisite: no subsequent sale of the drug). Examine the anti-tamper device at the time at which the drug is delivered to the public. Notify the competent authorities immediately if forgery or tampering is suspected.

3.2 Legal Obligations for Participants in the US Supply Chain

Manufacturer

Since 1 January 2015 Record transaction data ("Transaction Information") and transaction history ("Transaction History") at batch level; suspicious items (e.g. returns) are to be transferred in quarantine and their transaction history must be validated in the course of investigations.

From 27 November 2017 Serialize sales packaging and cartons of the drug.

From 27 November 2017 Verify serial numbers for salable returns (permitted for sealed cartons at carton level) and in the course of research on suspicious products; produce electronic records of all transaction details.

Repacker

Since 1 January 2015 Record transaction data ("Transaction Information") and transaction history ("Transaction History") at batch level; suspicious items (e.g. returns) are to be transferred in quarantine and their transaction history must be validated in the course of investigations.

From 27 November 2018 Serialize drugs. Only the receipt of serialized products is allowed.

From 27 November 2018 Transaction data are to be verified at the batch level, verify serial numbers on salable returns (permitted for sealed cartons at carton level) and in the course of research on suspicious products. Disclosure of transaction data is mandatory.

Distributor

Since 1 January 2015 Transaction data and transaction history are to be transmitted in the wider supply chain at batch level. Suspicious items are to be transferred in quarantine and their transaction history must be validated in the course of investigations.

From 27 November 2019 Only serialized products will be accepted.

From 27 November 2019 Verify serial numbers on salable returns (permitted for sealed cartons at carton level) and in the course of research on suspicious products; returns are to be allocated to their original transaction data. The transfer of transaction data is mandatory.

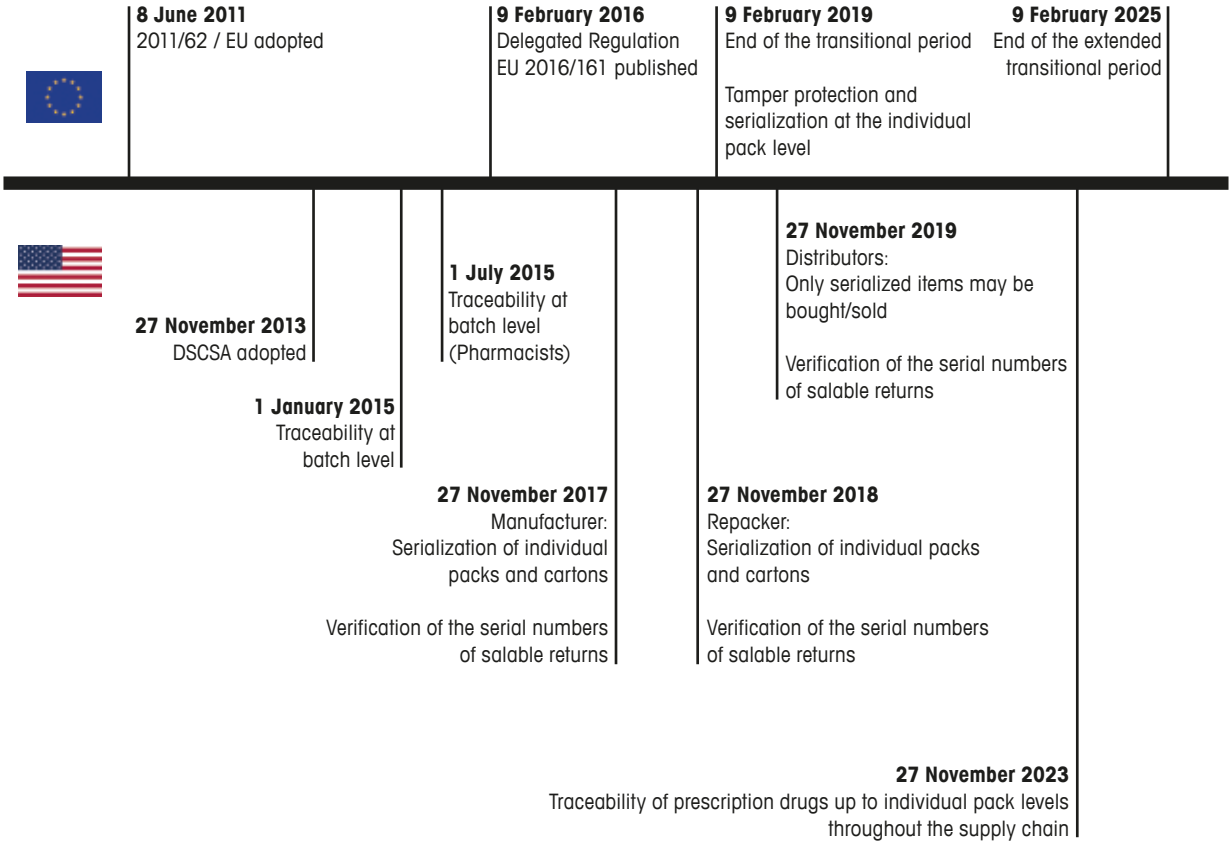
Pharmacist

Since 1 July 2015 Disclose transaction data and transaction history at batch level; suspicious items are to be transferred in quarantine and their transaction history must be validated in the course of investigations.

From 27 November 2020 Only serialized products may be accepted. Verify serial numbers in the course of research on suspicious products. Verification of the serial number when dispensing the drug is not required within the Enhanced System from 2023.

3.3 Implementation Deadlines*

The graph below provides a summary overview of the important milestones in the implementation of the counterfeit protection directive in the European Union and the Drug Supply Chain Security Act in the US.



* Belgium, Greece and Italy had already implemented systems for testing the authenticity of drugs before the entry into force of EU Directive 2011/62 / and may make use of an extended transition period to February 2025. It is anticipated that only Italy will use a prolonged transition period (as at: August 2016).

4 FMD/DSCSA: Similarities and Differences

4.1 FMD: Tamper Protection

To comply with the FMD pharmaceuticals manufacturers at the beginning of the supply chain have to ensure a means for protecting the packaging from being tampered with (Tamper Evidence). Its integrity when dispensing the drug documents that the packaging has not been opened along the supply chain. The DSCSA does not provide such a means of tamper protection.

Which Tamper Evidence Procedures are Permissible?
The FMD leaves it up to the pharmaceutical manufacturer which Tamper Evidence methods they select. The requirements to be met are specified in EN 16679.

What Should be Noted on the Packaging when Attaching the Tamper Protection?
Any potential tamper-proof seal must not impair the legibility of the prescribing information on the package. All information must still be legible even when the package is opened. Using opening aids such as perforations or opening tabs is permitted.

What Technologies are Available?
Currently, the most frequently used tamper evidence methods in the pharmaceutical industry are bonding and the use of self-adhesive seals. Adhesive dots (Gluing) cause irreversible damage to the carton on first opening due to their strong adhesion. To avoid the disadvantages of hot- and cold-melt processes – possible reversibility when heat sealing, long drying times for cold glue – adhesive combinations are recommended.

Self-adhesive seals are also already widely used. They are available in variants that visibly damage the carton's surface on opening or as void film seals which reveal a previously hidden element (e.g. a pattern, company logo) on first opening.

Further alternatives such as tamper protection on special folding structures or foiling have even lower market relevance due to their associated high process requirements and potential security deficiencies.

The **METTLER TOLEDO White Paper** "Pharmaceutical Tamper Evident packaging - are you prepared?" gives detailed information on the advantages and disadvantages of the available technologies as well as the EN 16679 standard.

Note: For more information on marking, verification and product safety, please see our white paper entitled:
"**Are You Prepared for EU Compliance?**".

For further information see: **www.mt.com/PCE-tamper-evident**

4.2 DSCSA: Documentation of the Supply Chain

An essential security component of the DSCSA is the precisely logged traceability of the drug across the entire supply chain. Infringements of the documentation requirements and violations of the registration and licensing regulations stipulate firm sanctions by fines, suspensions, license withdrawals and even imprisonment. The FMD in the EU prescribes no documentation by individual locations in the supply chain and focuses on testing for counterfeits when dispensing the drug.

What Should be Documented?
The FDA requires the mandatory documentation of all transactions. Documentation must distinguish between
- Transaction Information (TI)
- Transaction History (TH)
- Transaction Statement (TS).

What Transactions Must be Documented?
Transactions relating to the ownership or transfer of ownership of a product must be documented. Exceptions to the documentation requirements exist for, among others, the distribution of products for internal deliveries, deliveries between hospitals, public emergency rooms, and the distribution of samples, blood products, certain IV products and medical gases.

What information Must the Transaction Details Mandatorily Include?
- Name/identity of the drug
- The product's National Drug Code
- The product's strength and dosage
- Container size and number of containers
- Batch number (and, from 2023, including the Serial number)
- Transaction date
- Delivery date, if delivered more than 24 hours after the transaction date
- Name and address of the company and the trading partner to whom ownership is transferred.

What information Must the Transaction History Include?
- Record of all transaction data for any movements of the product reaching back to the manufacturer, in paper or electronic form.

What information Must the Transaction Statement Include?
Declaration in paper or electronic form, that the business unit which transfers the ownership, in accordance with the DSCSA:
- Is authorized
- Has received the product from a person who is licensed / authorized
- That the Transaction Data and the Transaction History obtained from the previous owner comply with the statutory requirements
- That this is knowingly not the supply of a suspicious or illegal product
- That the systems and methods used for product verification comply with the law
- That no false Transaction Data are knowingly being passed on and that there were no changes in the Transaction Data.

Are there Standard FDA Forms for this Purpose?
No. The FDA has, however, published a guide for this purpose on its internet site.

What Retention Periods Have to be Met?
TI/TH/TS documents must be kept for six years.

4.3 FMD: Unique Identifiers (Data Matrix Code)

The verification of the authenticity of the unique identifier stored in the Data Matrix code when dispensing ensures that the drug originates from the legal manufacturer or packer and has not been deleted from the central database. The standard check of the Data Matrix code on dispensing is an essential security component of the FMD. The DSCSA provides no comparable procedure when dispensing the drug and focuses on the protection of the supply chain. Tests are carried out on suspected counterfeits.

What Data Elements Must be Recorded in the Unique Identifier?

- Product code
- Serial number
- Batch number
- Expiration date
- National reimbursement of costs and identification number (optional).

What Information Does the Product Code Include?

The globally unique product code is used to identify the drug and contains at least the name, common name, dosage form, strength, pack size and type of packaging.

Are the National Reimbursement of Costs and Identification Number Mandatory?

Yes, this is mandatory if required by the Member State in which the product is to be marketed. If the number is included in the product code it does not need to be repeated in the unique identifier.

What Requirements are there for the Serial Number?

The probability of being able to derive the generated serial number must be less than 1 in 10,000. The serial number consists of a numeric or alphanumeric sequence of at most 20 characters which the company, or a company appointed by them, generates as per its requirements.

What Requirements Apply to the Encoding?

Manufacturers have to encode the unique identifier in a 2D barcode which complies with Data Matrix ECC200 standards for error detection and correction. Bar codes must comply with 16022 ISO/IEC: 2006. Identifying and decoding the data element must be possible with standard scanners. The requirement is satisfied by unique identifiers complying with the ISO/IEC 15418: 2009 coding standard.

Note: For more information on coding, please see our white paper entitled:
"**Making Codes Readable**".

For further information see: **www.mt.com/pce-making-codes-readable**

For how long Must the Identifier be Unique?

The character string derived from the combination of product code and serial number must be unique for each drug package for at least one year from its expiry date or at least five years from the marketing of the product. The decisive factor here is the longer period.

Must a Read Check of the Codes be Carried out?
Yes. The manufacturer who affixes the security features is required to check that the 2D barcode with the unique identifier is readable and contains the required information. The read check ensures that the code is present, the correct symbols were used and that the content matches the specifications. Packages without a code or with the wrong contents must be ejected. The readability of the code must be checked throughout the supply chain and during the usage cycle. This requirement is satisfied at a print quality of at least 1.5 in accordance with ISO IEC 15415 if the drug's manufacturer has taken into consideration possible aging and wear effects on printing.

Does the Read Check also Include Clear Text Printing?
Yes. Checking clear text printing with the code content is also part of the read check because this information is part of the required components of the unique identifier.

Can the Manufacturer Remove or Replace Security Features that Have already been Attached?
Yes. However, they will have to check the integrity of the anti-tampering device and the authenticity of the unique identifier beforehand and deactivate the Data Matrix code.

Can a Deactivated Data Matrix Code be Reset back to Active Status?
Yes. In this case the reset has to be done within ten days after deactivation of the unique identifier. Manufacturers, distributors and those authorized to dispense drugs to the public are generally entitled to do so.

What Should be Noted when Applying Equivalent Unique Identifiers?
Those responsible for marketing the drug must advise the hub of the batch number(s) of repackaged or relabeled packages and the unique identifier of the packages for each re-packaged or re-labeled batch of drugs which will be provided with equivalent unique identifiers.

Can Distributors Deactivate the Data Matrix Code?
Member States may - to take account of the supply chain in their countries - require distributors to check the security features and disable unique identifiers before delivery to certain individuals and entities. These include:
- Dentists, paramedics, doctors, optometrists, opticians, veterinarians and retailers of veterinary drugs and those authorized to dispense drugs who do not work in a pharmacy or health facility
- Prisons, schools, hospices, nursing homes, the armed forces, the police, government institutions such as civil protection and disaster relief entities, universities and higher education institutions.

Which Goods Do Distributors Have to Check?
Distributors have to check all packages of drugs which are not supplied directly by pharmaceutical companies, or on their behalf. So a distributor has to test each drug package that they acquire from another distributor or that is returned by a pharmacy for authenticity.

How Must Distributors Check Drugs that Have a Higher Risk of being Counterfeits?
It is up to the distributor to decide whether to read single unique identifiers or - if available - aggregated codes. Furthermore, it is up to them when they test all the unique identifiers of drugs in their physical possession which have a higher risk of being counterfeits.

How are Packages Dispensed in Multiple Countries to be Encoded?
Multi Country Packs carry several national product numbers for reimbursement purposes as well as for merchandise management purposes and other various country-specific information. The definition of the data elements for Multi Country Packs is still pending. This also applies to the plain text information (as at: August 2016).

How are Hospital Packages to be Encoded?
Hospital packages are encoded in the same way as for normal pharmacies. When hospital packages consist of clinical components the hospital package and not the clinical component is considered to be the sales packaging. This means that the Data Matrix code with the unique identifier is applied to the hospital package and not the clinical component.

4.4 DSCSA: Three-pronged Security Design

DSCSA's security design is to protect patients against drugs illegally introduced into the US supply chain and is based on the cornerstones of **serialization**, **verification** and **information exchange**. The scheduled ten-year implementation period will be completed in 2023 and is roughly divided into three phases:

These three phases involve the rollout of several features which are intended to improve the security of the drug supply chain.

Security Factor Serialization
- SNI (Standardized Numeric Identifier), to clearly identify individual packs of prescription drugs or sealed cartons with corresponding individual packs with the same content
- No purchase/sale of unserialized products
- Gradual implementation from 27 November 2017.

Security Factor Verification
- Check if the Product Identifier is attached or printed and the individual packs or the sealed carton with individual packs has the same content with the SNI or batch number and expiry date
- Systems and processes for validating the transaction data, transaction history and transaction statement for products in possession
- Verification at batch level.

Security Factor Information Exchange
- Mandatory feedback to requests for information within 48 hours in the event of a suspicious product for inquiries on transaction data, transaction history or transaction statement (since 2015)
- Mandatory notification within 24 hours of illegal drugs at batch level
- Verification of Product IDs/SNIs at the individual pack/carton level within 24 hours (from 2017)
- Verification at the individual pack level, including SNI and feedback to requests for information within 24 hours.

What Should be Noted Regarding Product Traceability?
Since 2015, manufacturers, distributors, repackers and most delivery points - mainly pharmacies - provide information for each purchase/sale at batch level within the US market throughout the supply chain. These include, for each change of ownership, the transaction data, transaction history and transaction statement.

What Should be Noted Regarding Product Verification?
Since 2015, manufacturers, distributors, repackers and most dispensaries - mainly pharmacies - have maintained appropriate systems and processes that will enable them to verify the Product Identifier on certain prescription drugs. They must be able to:
- Answer verification inquiries on suspect products

- Notify trading partners and the FDA regarding any faulty or illegal products
- Respond to alerts for incorrect or illegal products.

Is there a Standard Way to Verify Serial Numbers throughout the Supply Chain?
No. Verification of serial numbers as a proactive routine measure is not required, with the exception of returns. Verification is for checking suspicious products. Routine verification could, however, take place from 2023 under the electronic system.

What Should be Noted Regarding Product Identification?
Manufacturers and repackers have to apply a Unique Product Identifier (2D barcode) on certain prescription drugs packages in the course of serialization. From 27 November 2019 distributors may only distribute products that carry the Unique Product Identifier. From 27 November 2020 delivery points such as pharmacies will accept only drugs with a Unified Product Identifier.

How Does the DSCSA Affect Existing Federal Regulations?
The DSCSA already recognizes existing federal laws on traceability and pedigree and state laws for the licensing of distributors, provided they do not conflict with the provisions of the DSCSA. Examples of US states that have already enacted appropriate legislation to place them on the federal level are California and Florida. Existing regulations at state level will remain valid as long as they do not contradict the DSCSA. The FDA regulations are binding as nationwide US national standards.

What Drugs Have to be Serialized?
Primarily prescription drugs in dosage form, for example, capsules and tablets. However, the DSCSA provides for a number of exemptions, such as blood or blood components provided for transfusion, radiopharmaceuticals, contrast agents, certain IV products, medical gases and homeopathic drugs.

Is there a Mandatory Drug List?
No. Manufacturers are therefore faced with the very detailed task of matching the characteristics of their products with the provisions of the DSCSA. The general rule is: DSCSA compliance is not required for any drug which is not classified by the FDA as a prescription ("Rx only").


Different strategic directions of the FMD and the DSCSA

While in the US serialization should allow all the activities of a preparation over the entire value chain to be reproduced - a check on the authenticity of the product is made only in case of suspicion- Europe takes another route: Here the focus is on the verification of the authenticity of a product prior to its being delivered to the buyer, while the route to the buyer is not fully documented.

Both have their advantages and disadvantages. Many market participants expect that in Europe - as in other countries such as China, Korea and Turkey - at a later stage, there will be aggregation of prescription drugs, which then also enables the tracking of all serial numbers in the transport chain.

4.5 FMD/DSCSA: Data Matrix Code and Product Identifier

2D-Barcode (Data Matrix Code)

Sample of a 2D Barcode

The 2D barcode stipulated by the FMD is used for verification of the unique identifier. In accordance with the FMD manufacturers are also obliged to print the product code and serial number in a human-readable format.

Can the 2D Barcode Hold Further Information in addition to the Unique Identifier?
Yes, this is permitted where the competent authority so permits under Title V of Directive 2001/83/EC.

Is the Imprint of Other Barcodes for Identifying and Verifying Authenticity Permitted?
No, this is inadmissible for drugs, which must carry the security features.

Is the Printing of Additional 2D Barcodes Allowed?
Yes. It is permissible to apply other barcodes for example: the Central Pharmacy Number Pharmazentralnummer (PZN) in Germany. Important: However, these barcodes cannot contain the unique identifier that is used to verify the authenticity or the identity of the drug.

Can Drugs not Subject to Verification Contain a Serial Number in the 2D Barcode?
No. Optionally the batch number and expiry date may be encoded. However, the encoding of a serial number in the 2D barcode is prohibited.

Can Non-prescription Drugs Carry the Security Features?
No. Important: Whether a drug is available on prescription can vary between EU Member States. This means that a drug may be required to use the security features in one country, whereas the security features may not be applicable in another Member State. As a consequence the operational implementation of this will have a particularly significant impact on Multi Country Packs.

Product Identifier & SNI

NDC		Seriennummer
11111 222 33	+	12345678901234567890

Sample of a Serialized National Drug Code (SNDC)

The DSCSA defines a so-called Product Identifier which is to be attached by manufacturers of prescription drugs at the latest from 27 November 2017, as well as by repackers onto individual packs and cartons from 27 November 2018.

What Information is Provided in the Product Identifier?
The Product Identifier includes the National Drug Code (NDC), a serial number, the lot number and expiration date. It includes a machine-readable tag as a 2D Data Matrix code at pack level, and a linear or 2D Data Matrix code at carton level. The information must be applied in a human-readable format.

What is the Function of the Standard Numerical Identifier (SNI)?
The FDA guideline for the standardization of the numerical identifier of drugs describes the SNI, based on which the full traceability of most prescription drugs should occur - except e.g. by ISBT 128-labeled biological products such as stored blood. The SNI included in the Product Identifier is the central component for the identification, validation, authentication and traceability of prescription drugs in the supply chain.

What Components Does the SNI Contain?
The SNI combines for all the relevant medicines - including their packaging configuration - the corresponding National Drug Code (NDC) in accordance with 21 CFR Part 207 plus a one-time serial number generated by the manufacturer or repacker.

What Requirements Apply to the Serial Number?
The serial number can consist of a numeric or alphanumeric sequence and should contain no more than 20 characters. Prior to the publication of the FDA guideline most prescription drugs already had an NDC.

Where is the Human-readable Information to be Placed on the Packaging?
Depending on the dimensions of the package the human-readable data elements should be printed next to the 2D barcode. This is to allow deactivation of a unique identifier in the case where the 2D barcode is unreadable.

Are More Data Elements of the Unique Identifier to be Printed in Plain Text?
The national reimbursement number or another number for identifying the product is to be printed, if this is from a Member State in which the product is to be placed on the market and is required and this number is not printed elsewhere on the packaging.

Are Exceptions to this Permissible?
Yes. The FMD requirements for printing human-readable data elements do not apply if the sum of the two longest dimensions of the package is 10 centimeters or less.

Combining a serial number up to 20 digits long with the NDC creates a numerically large enough set for duplicate-free marking. The FDA refers to this identifier for use with prescription drugs also as a serialized NDC (SNDC).

On what Types of Packaging is the Product Identifier to be Applied?
The general rule is: Manufacturers and, in the wider supply chain, repackers must apply Product Identifiers at "package level" in accordance with the FDA specifications for the SNI: In the guidelines for SNI product identifiers, the FDA defines a "package" as the smallest unit in the exchange of goods between US states which is intended for retail sale in pharmacies or other dispensaries. The definition of a unit intended for retail sale is provided by the FDA's guidelines for labeling, which governs retail distribution of pharmaceuticals.

SecurPharm Case Study Implementing Recommendations in Germany

SecurPharm is a German organization which is spearheading efforts to prepare pharmaceutical manufacturers for the implementation of serialization in the EU. The organization has published a set of guidelines for the use of data matrix codes in serialization applications.

Data Matrix Code: Data Matrix barcode depending on square or rectangular package size. Module size may vary between 0.25 mm to 0.615 mm, size scalable within this range.

Clearances: Surfaces touching the Data Matrix Code must be kept free of further printing. Code rest zones must be observed in order to ensure an acceptable first reading rate.

PPN-Emblem: "PPN" emblem on Data Matrix Code. Mandatory for all packages which carry a second 2D code. Minimum distances to the code (code rest zones) must be observed. The PPN emblem is used to identify the code for automatic detection and will be maintained until the adoption of different uniform international labeling.

Plain text information: PZN in plain text with Code 39, batch number, expiry date and product code and serial number. If the product code and serial number are printed on two lines, the first line contains the product code, the second line contains the serial number. "PC:" is the product code, "SN:" the serial number, each followed by the relevant number. The Product Code can be applied on first printing, because it does not change each time the package is opened. For batch number and expiration date the legally prescribed drug labeling requirements shall be followed and printed fully with no abbreviations, except for batch number ("Ch.B.") and expiration date ("best before"). Exception: Suitable abbreviations, such as "b. before" are permitted for up to 10 milliliters nominal quantity and ampules which contain only a single use unit.

How are Packages Split into Subsets?
In this case each subset is associated with a new SNI, thus creating a new Product Identifier to be linked with the SNI of the original package.
Example: A repacker receives a carton with eight ampoules and packs them into two cartons of four ampoules for retail sale. In this case, they have to create two new SNIs or Product Identifiers for the two cartons and link them with the original manufacturer's SNI.

Does the SNI Contain the Expiry Date and/or the Lot or Batch Number?
No. The expiration date and/or lot or batch numbers are not part of the specifications recommended by the FDA for the SNI, since, in the FDA guidelines, this information is for the identification of each drug; i.e. prescription and non-prescription drugs are already included. The SNI can supplement databases that contain this and other related information. The aim of this approach is to ensure that the SNI is not too long or too complex.

Is the Inclusion of the Expiration Date and/or Lot or Batch Number Prohibited?
No. If a manufacturer or repacker chooses to include the expiration date and/or lot or batch number in the SNI, they must ensure the resulting number continues to allow participants in the supply chain to recognize and use the SNI. So, for example, expiry date and/or lot or batch number can be included in the SNI in accordance with the GS1 standards for use of Global Trade Item Numbers (GTIN).

Must the SNI be Printed in a Human-readable Format on the Package?
The FDA recommends, but does not require, that the SNI is printed in plain text, so that it can still be read in the event of the non-availability of electronic means, such as a software or hardware failure.

Where is the SNI to be Placed on the Package?
The FDA does not specify requirements for placing the SNI. As the NDC is already printed in clear text on the package, the serial number can be printed as plain text elsewhere on the product packaging. This must be done so that there is no mutual interference between the readability of the SNI and the NDC. The general rule is: Any placement of the SNI on the package must not lead to any adverse effects; a simple scan and read of the SNI must be possible without damaging the packaging or the product.

How Compatible is the SNI as Recommended by the FDA to International Standards?
The FDA has worked closely in the development and recommendation for a serialized NDC and SNI with all stakeholders in the supply chain and GS1 in the development of the standard. The SNI is thus compatible with the GTIN, which is used by dozens of countries to uniquely identify pharmaceutical products.

4.6 Protection Against Counterfeits

Checking the Identifier

Verification of unique identifier authenticity is carried out by comparing the data stored in the data storage and retrieval system with the unique identifier. To disable the unique identifier, an authorized connection via the national or supranational data storage with the European hub is used.

Are the Sale or Transfer of Drugs with a Disabled Unique Identifier Permissible?
The distribution and delivery of drugs are subject in this case to restrictive regulations. The most frequently allowable scenarios in practice are:
Distributor deactivates the unique identifier in order to:

- Export the product from the EU market
- Take into account the particular characteristics of the supply chain in individual Member States
- Withdraw the product from the market and/or to deliver it for disposal.

Owners having marketing authorization to place free samples on the market deactivate the unique identifier before delivery to persons who may prescribe the drug. Free samples must be marked as such on the European hub.

What to Do in Case of Technical Problems with the Delivery of the Drug?
Record the unique identifier and deactivate it once the technical issues are resolved.

Is it Permissible to Reset the Status of a Deactivated Unique Identifier Back to Active?
Yes, but only if the person resetting the status has the same authority as the person who performed the deactivation and must work in the same operational area as them. The status reset must be made within ten days of deactivation.

How is the Delivery of Subsets Handled?
On first opening the package, both security features should be checked and the unique identifier must be disabled.

Behavior in the Event of Suspicion

Manufacturers, distributors, repackers and those placing drugs on the market (mainly pharmacies) must quarantine and immediately inspect any drugs that have been identified as suspect. Suspect is defined as a drug which is identified as fake, unauthorized, or potentially dangerous. The FDA and other stakeholders must be notified upon discovery of an illegal drug.

What Measures Should be Taken in this Case?
The inspection must include validation of the transaction data. The inspection must also include verification of the serial number of the suspected product if the company has started to receive serialized products. Exception: Pharmacists should verify the serial numbers on three packages or 10 percent of all the suspect products, whichever number is larger.

What Safeguards are Involved until the Enhanced System is Implemented in 2023?
The Enhanced System specifies the electronic traceability of products at the individual pack level. Electronic data exchange provides the transaction data for every sale for certain prescription drugs. The Product Identifier is verified at the level of the individual pack.

Does the 2023 Model Provide for Authentication when Dispensing to the Public?
No. When the Enhanced System 2023 has been successfully implemented electronic traceability focuses on the purchase and sale of each package along the supply chain. Verification of the serial number prior to dispensing to patients is not required.

4.7 FMD/DSCSA: Management of Serialization Data

European Hub

The uploading of data required by the FMD into the data storage and retrieval system shall be completed before the marketing of the drug; the information must then be kept up to date.

Where Will the Information be Stored?
In all national and supranational data stores for the/ those Member State(s) in which the drug is to be marketed.

Who Has Access to the Data Store?
Manufacturers, distributors and those authorized to supply drugs to the public or authorized persons.

What Data is to be Uploaded?
The data elements of the unique identifier, coding scheme of the product code; name, common name, dosage form, strength, packaging type and packaging size, Member State(s) in which the product is to be placed on the market; name and address of the manufacturer who affixes the security features, name and address of the owner of the marketing authorization; list of distributors authorized to store and distribute the drug on behalf of the manufacturer. The data store contains a complete log (audit trail) of all the actions related to a unique identifier, and the user who carried out this action.

Are there Safeguards against Duplicates?
Yes. The national or international data store prevents uploading or storing a unique identifier that carries the same product code or serial number as another unique identifier which has already been stored.

How are Batch Recalls Dealt with?
The distributor shall ensure that the unique identifier of the drug that is to be recalled or withdrawn from the market is activated in the data store for the Member State(s) where the drug is to be taken off the market. The identifier is updated to indicate the product has been recalled or withdrawn from the market.

Interoperable Electronic System

By 2023, all updates of transaction data must be made electronically to the level of the smallest packaging unit. The transaction data must include the Product Identifier / SNI at the individual pack level. Systems and processes for verification at the individual pack level, including the SNI, must be implemented by the 2023 deadline. The systems must keep track electronically of the collection of transaction data for each transaction back to the manufacturer, so as to investigate suspicious items, carry out checks and/or lead the way in conducting product recalls.

How Will the Electronic Transmission of Data be Carried out in 2023?
As of August 2016, details of electronic tracking at the individual package level has not been defined, particularly the methods for data management and transmission. Unlike non-US models a single government repository is unlikely. It is expected that advanced data housing solutions will emerge from the industry.

What Licensing Rules are Distributors Subject to?
The FDA has developed national standards for the licensing of drug distributors and drafted a nationwide system for licensing drug distributors for states whose systems do not meet the national standards. Since 1 January 2015, distributors have notified their licensing status and their contact information to the FDA. This information is available in a publicly accessible database.

What Licensing Rules are Logistics Partners (3PL) Subject to?
In the future, logistics partners need a state or federal license. The FDA has drafted national standards for the licensing of logistics service providers for states whose systems do not meet national standards. Logistics service providers are classed as external logistics partners who provide warehousing and logistics services in the distribution of medicines.

What Record-keeping Obligations Does the Manufacturer Have?
Manufacturers are responsible for establishing a serial number repository collecting the generated on-line data so they can be exported to the European hub. The manufacturer who affixes the security features is required to monitor and store every action they perform in connection with the unique identifier. This applies for at least one year from the expiration date of the pack, or five years from the pack being placed on the market. The longer period is relevant.

How Does the European Hub Manage the Handling of Multi Country Packs?
In this case the market in which the drug will be delivered to the public may not be known while it is in production. It is envisioned that the European hub will send the serialization data to the national systems of all countries where delivery could occur. Once the product has been delivered in one of these markets and the unique identifier has been disabled, this information on the European hub is routed to the other national systems and the drug is labeled accordingly.

Transitional Period: How are Stock Items Dealt with?
Medicines that have been approved in a Member State for sale or distribution before the date of application of the Regulation without the security features and were not repackaged or relabeled, may be marketed, sold and delivered to the general public in that Member State until its expiration date.

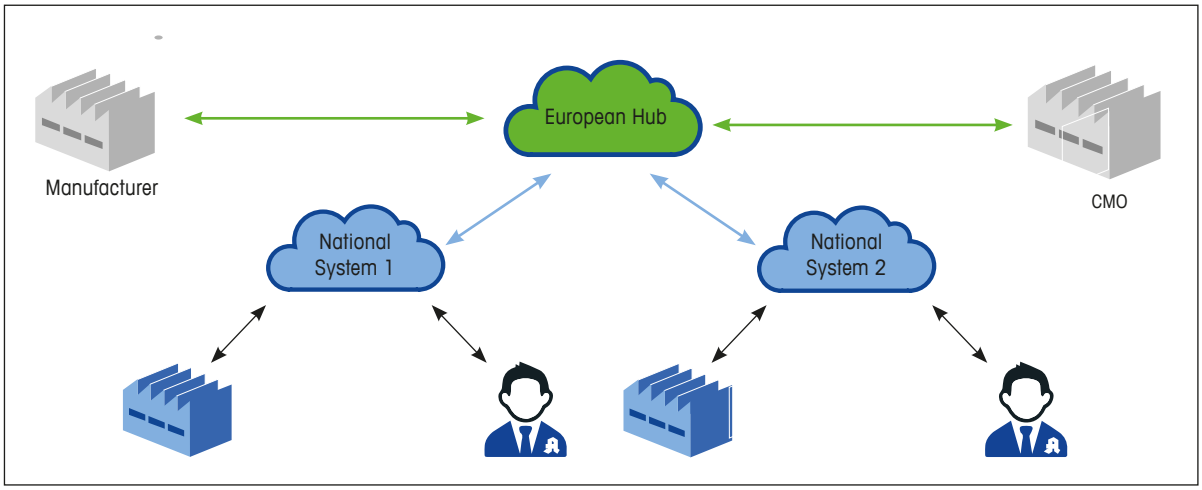


Fig. 4.7: The European Hub's Management of Serialized Data

4.8 Aggregation

Is Aggregation of Serialization Data Required?
No. Neither the FMD nor the DSCSA call for the aggregation of data. However, aggregation of data is required operationally in view of the traceability requirements at the item level in the 2023 US supply chain. Downstream trading partners could in theory request aggregated data ahead of time. So, in practice, this is already demanded by manufacturers from contract manufacturing organizations (CMOs).

5 Practical Tips

Coding Recommendations

The following recommendations are designed to enhance the readability of the serial number and batch number, thus minimizing the risk of machine as well as human reading errors.

Codes should:
- Avoid strings that contain both uppercase and lowercase letters
- Avoid using characters with a high likelihood of confusion (e.g. "I, j, l") to prevent human reading errors
- Avoid special characters in order to reduce the risk of misinterpretation of the code
- Use dashes, underscores or periods for separators within a batch label
- Limit affixing additional codes to what is necessary in order not to interfere unnecessarily with the process security.

The coding of long URLs lengthens the code considerably and may reduce the reading rate. Detailed information on coding recommendations includes the **METTLER TOLEDO White Paper "Making codes readable."**

Packaging Design

Whether for compliant mounting of tamper protection in accordance with the FMD or implementation of the placement, formatting and spacing requirements for the 2D barcode, serial number and batch name in accordance with the FMD and the DSCSA: each package to be serialized must undergo testing if any changes are required in any directives or legally compliant packaging design. Among other things the following must be tested:

- Compliance: Where and how do I put a 2D barcode, serial number and batch number, are they all necessary, can plain text information in human-readable form be mapped with the previous design? Will minor revisions suffice or is a complete redesign necessary?
- FMD: What effect does the attachment of tamper protection have? As a consequence, are design compliance adjustments required?
- Is the old/new design representable in the existing/future planned inspection systems?

Production Line and Data Infrastructure

- The right data at the right time at the right place: Build and expand the coding and serialization capability step by step from line level through site level to enterprise level, thus taking into account that: systems and methods need to cope with much more demanding requirements for variable coding on the line
- Schedule sufficient staff training. Tamper protection in accordance with the FMD has far-reaching effects for existing processes: Handling rejected products (e.g. because of faulty pressure, damaged packaging, packaging not replaceable), documentation, training in dealing with new coding and inspection systems
- Aligning serial number generation so that line speed does not suffer
- Provide IT resources for testing: Data volumes increases significantly with serialization
- Do not lose sight of the fact that the complete solution includes printers, a database and an IT environment
- Evaluate the effects of the tamper on OEE and workflow early on - prime example: assembling a national leaflet
- Which product, when, and for what market? Demand, match stock management with the serialization date
- Agree timing, milestones and communication in the supply chain with all business partners and organizations affected by serialization.

6 Conclusion

Both the FMD as well the DSCSA require inspection systems with the ability to print serialized 2D codes to verify them and which can handle communication with a centralized database/ERP system.

How can today's investment decisions be made future-proof?

Manufacturers who make their production lines fit both the requirements of US serialization from 27 November 2017 as well as the EU's FMD requirements from 9 February 2019 will be in a position to comply with the pending 2023 DSCSA specifications.

It is recommended that architectures for both serialized and non-serialized items are built which are able to reflect globally interoperable standards adequately. It is especially important to opt for inspection solutions both for software (interfaces, data storage, etc.) and hardware (cameras, sensors, etc.) that have the most flexible expansion and migration capabilities.

International companies are advised to build a serialization solution including the aggregation of all standards outside the US and Europe. In the event that the scope is extended or the marketing of a product is expanded no further retrofitting of lines will be required.

Sources and Resources

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Checkweighing

Vision Inspection

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