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THE EUROPEAN UNION FALSIFIED MEDICINES DIRECTIVE – IMPLEMENTED SAFETY FEATURES

SWAPNA PRIYA S*, KOUSHIK Y AND RAMA RAO N

Department of Pharmaceutical Regulatory Affairs, Chalapathi Institute of Pharmaceutical Sciences, Chalapathi Nagar, Lam, Guntur- 522034

***Corresponding Author: Swapna Priya Suryapaga: E-Mail: swapnasuryapaga@gmail.com**

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ABSTRACT

Falsified drugs pose a challenge to public health in the case of serious adverse effects, the association of harmful ingredients with other medicines, little change in the disincentive of health conditions to take prescription medicines and lack of confidence in the health care system. There is no system at present that helps consumers to check where a drug comes from The EU Falsified Medicines Directive (FMD) aims to prohibit falsified medicines from accessing and reaching patients in the legal supply chain. This impact review acknowledges the versatility of Article 23 under the FMD's safety features policy. The policy of "safety characteristics" includes a unique identifier and tamper- evident characteristics to be applied to prescription medicines to prevent damage from falsified drugs to persons in the UK and to decrease the incidence of falsified medicines in the legal supply chain.

Keywords: EU FMD, Falsified medicines, Falsified medicines Directive, Safety features, Supply chain

INTRODUCTION

In May 2017, in place of the commonly used word, spurious/falsely-labelled/falsified/counterfeit, the World Health Organisation (WHO) adopted the term substandard and falsified (SF) medicine (SFFC). Both substandard and falsified medications are covered by the current term, SF. Substandard or 'out-of-specification' drugs, according to the WHO, are medicinal products that do not follow either their quality requirements or specifications, or both. Falsified drugs are

"medical products that misrepresent their identity, composition or source intentionally/fraudulently" and exist in illicit international internet markets, in low- and middle-income countries (LMICs) and high income countries (HICs) **[1]**.

Falsified medications are fake medicines that are passed off as actual, approved authorised medicines. The European Union (EU) has a strict legislative system for the licensing, manufacture and delivery of medicinal products, based on the Falsified Medicinal Products for Human Use Directive, which permits only licensed pharmacies and authorised stores to sell medicinal products for sale, including legitimate online sales. The European Medicines Agency is working actively on enforcing these laws with its allies.

Medicines that are falsified may:

- Contains low-quality ingredients or in the wrong doses;
- To be mislabeled purposely and fraudulently with regard to their name or source;
- Have had Fake packaging, wrong ingredients or poor concentrations of active ingredients

Falsified pharmaceutical products do not proceed through the usual evaluation of quality, safety, efficacy protection and effectiveness review needed for the EU approval process. They may be a health hazard regardless of this.

With more and more drugs now being falsified, the phenomenon of falsified medicines is on the rise. These include pricey medications, such as anticancer drugs, and high-demand medicines, such as antivirals **[2]**.

A classification of medicine counterfeiting practices is given in **Table 1** below that reportedly happened in Europe **[3]**.

MEDICINE COUNTERFEITING PRACTICES: Finished medicinal products
• ***Identical copy*** **- identical formulation with packaging and labelling that is hard to differentiate from the original**
• ***Pure counterfeit*** **- altered/replaced ingredients with similar packaging (but either no/different/wrong dose API or excipient)**
• ***Hybrid counterfeit*** **- re-use of components/refilling (e.g. genuine containers [ampoules, bottles, vials, syringes] and packaging with substitute or no API)**
• ***Illegal relabelling/repackaging*** **- genuine formulated product falsely repackaged/relabelled as being from the original manufacturer and intended for the same or diverted to a different market than originally intended by manufacturer (also includes use of fake pricing labels and products claiming wrongly to be an original product e.g. use of well-known name or trademark)**
• ***Diversion and illegal trade*** **- of genuine medicinal products with genuine packaging and labelling (whether or not through the internet)**
• ***Unpackaged medicinal products*** **- e.g. wholesale/retail of medicinal products without the primary authorised packaging**
• ***Placing a non-authorised medicinal product on the market*** **- exploitation of regulatory weaknesses concerning regulation of personalised medicine trade within the EC borders**
• ***False documentation*** **- e.g. granting a Certificate of Suitability (CoS or CEP)* by regulatory authorities without the given company being audited, false CEP, incorrect status on import documentation**
• ***False MAA*** **- entire marketing applications is sold and used; their contents do not have any relationship with the actual operations involved in the manufacture of the API or dosage form**
• ***Waste/expired product re-entering the market*** **- includes repackaging and relabelling of expired products**
MEDICINE COUNTERFEITING PRACTICES: Active pharmaceutical ingredients and excipients

• ***API procurement from uncontrolled/non-GMP origin*** **- done by some authorised FP manufacturers because uncontrolled API source is cheaper**
• ***Illegal API relabelling/repackaging*** **- unauthorised API material may also be shipped in containers labelled with the name of a different API**
• ***'Ghost API manufacturing plant'*** **- API (possibly not produced via the registered manufacturing process) not manufactured by the 'registered producer' is sold to FP MAH (who may be unaware of this fact, as API label mentions only the authorised manufacturer; a broker/trader may play a crucial role in this practice)**
• ***'Ghost API supplier'*** **- MAH purchases API willingly and knowingly from a different manufacturer than that specified in the MA (in this case the manufacturing process will normally differ from that described and authorised in the MA)**
• ***'Paper curtain'*** **- API manufacture performed through different process than that specified in the MA (a double documentation system may be used at the manufacturing site: one hidden set containing the true data and another set containing faked data that comply with authority requirements and regulations; such documentation systems may even be in place at a site where the API is not manufactured at all)**
• ***'Authorised facades'*** **- manufacturer/trader with approved CEP and DMF supplies API material from a large number of unauthorised manufacturers (all labelling mentions only the authorised manufacturer. This set up is believed to be widespread regarding API material imported from China and possibly also India. In addition forged CoA and other forged documents will also be used in such situations)**
• ***Illicit intermediate production*** **- unauthorised API materials from obscure sources are blended with the registered API material**

Legal Framework

For the licensing, processing and sale of drugs, the EU has a clear regulatory system. Only licensed pharmacies and authorised stores are permitted to sell pharmaceutical goods for sale at the end of the delivery chain, including legal purchases over the internet.

In July 2011, by introducing a new Directive 2011/62/EU on falsified medicines for human use, the EU improved the safety of patients and consumers. On 21 July 2011, the directive came into effect. In January 2013, Member States had to begin implementing their initiatives. This directive is meant to prevent falsified medicines from entering the legitimate supply chain and reaching patients.

THE FALSIFIED MEDICINES DIRECTIVE 2011/62/EU

The Falsified Medication Directive 2011/62/EU (hereinafter also referred to as the 'Directive') was adopted by the EU Council on 27 May 2011 and published in the Official Journal of the European Union on 1 July 2011 as a measure to resolve the increasing number of cases of pharmaceutical fraud in the European Union last year. The latest Directive 2011/62/EU on falsified medicines includes revisions to Directive 2001/83/EC and is divided into 6 articles:

Article 1: describes the modification to directive 2001/83/EC.

Article 2: defines the latest dates by which the modifications should be brought into force.

Article 3: deals with the report by the commission to the European parliament and to the council on the effectiveness of these modifications

Article 4: deals with the obligation of the commission to study the technical options for the unique identifier of the safety features, modalities of verification of the authenticity and repositories system.

Article 5: defines the date when the directive shall enter into force

Article 6: deals with to whom this directive is addressed.

The EU directive introduces the safety and strengthened control measures across Europe to prevent the entry of falsified medicinal product into the legal supply chain and to reach patients such measures include:

- Obligatory safety features on the outer packaging of medicines to demonstrate that they are authentic such as serialization number
- Obligatory logos, which must be placed on website of legal online pharmacies with a link to official national registers.
- Obligations for manufacturing authorization holder to report any suspicion of falsified medicines
- Strengthened requirements on the control and inspections procedures of active pharmaceutical ingredients (API).
- More stringent record keeping requirements for wholesale distributors **[3]**.

By applying new policies which can be grouped into four main pillars, it implements harmonized protection and enhanced control measures across Europe. They are:

1. Safety features of medicines

- As of 9 February 2019, marketing authorized holders are expected to put on the packaging of certain prescription medicinal products and some over-the-counter medicinal products in the European Union two protection features: a unique identifier (a 2-dimensional barcode) and an anti-tampering device in accordance to Delegated Commission Law (EU) 2016/161. The list of pharmaceutical products subject to this provision is contained in the annexes of the legislation.
- Manufacturers can submit to a central EU registry the details found in the unique identifier for each person medication. The registry is part of the framework of end-to-end verification of pharmaceutical products implemented by the legislation. Wholesalers may also need to scan medicines at different points of the supply chain to validate their validity, based on the source of the medicine. At the end of the supply chain, pharmacies and hospitals will then scan each medicine to verify its validity and check it out of the repository before dispensing them to patients.

- This safety features will ensure the authenticity of medicines for the benefit of consumers and companies, and will improve the security of the supply chain of medicines, from suppliers to dealers, pharmacies and hospitals.
- An action strategy, including regulatory criteria and timelines, has been prepared by the EMA and the European Commission to direct applicants and marketing authorisation holders of centrally approved medicines to fulfil the following requirements:
- Implementation strategy for the adoption of safety features for packaging of centrally authorized human-use medicinal products
- The product information templates for human medicines have been updated by EMA to permit companies to implement the new rules

2. Supply chain and good distribution practice

- The Directive incorporates new wholesalers' obligations and a description of brokering operations, as well as new brokers' responsibilities. Relevant provisions for brokering practices are contained in the amended good-distribution-practice guidance of the Department.
- Information on good distribution practice is now included in the Eudra-GMDP index (GDP).

3. Active compounds and excipients

- From July 2013, all active substances manufactured outside the EU and imported into the EU had to be accompanied by a written confirmation from the exporting country's regulatory authority.
- These statements shall be given per manufacturing facility and per active substance and shall ensure that good manufacturing practice (GMP) requirements similar to those in place in the EU are met. A number of countries have now dedicated themselves to giving confirmations in writing
- These written confirmations would not need to be issued by exporting countries with a 'equivalent' regulatory structure. Together with the Organisation and the Member States, the European Commission is evaluating the regulatory structures of countries applying for 'equivalent' status.
- The European Commission maintains a website describing the status of the

applications received: Quality of medicines and GMP.

4. Internet Sales

- The required logo to appear on the websites of legally licensed online pharmacies and licensed retailers in the EU has been adopted through the Directive.
- As part of the steps to tackle falsified medicines, the EU has adopted a common logo for legally operating online pharmacies/retailers in EU countries as shown in **Figure 1**. The logo ensures that the websites are legitimate and guarantees the safety of the products.
- This logo will allow Identification of authorized online pharmacies and licensed retailers selling real, certified medicines for patients and customers. Clicking on the logo can connect to the websites of the national regulatory authority, which will list all legally operating online pharmacies and registered retailers in their respective countries.
- The Implementing Regulation laid down the current logo entered into force in July 2014, prompting the Member States to prepare for its application by July 2015.
- Member States will launch efforts to increase awareness of the logo and the risks of falsified medicines until the Regulation has been implemented **[2]**.

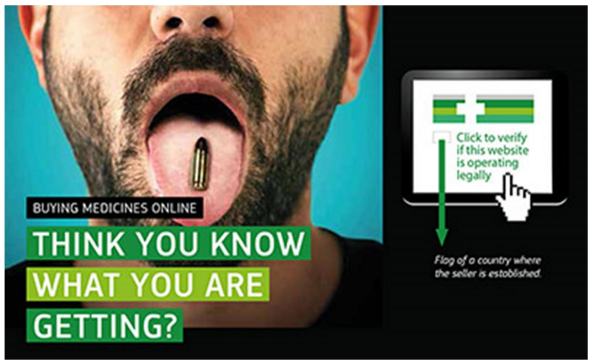


Figure 1 : common logo for legally operating online pharmacies

HOW DOES FMD WORK: WORK FLOW PROCESS

Each manufacturer will generate randomised unique identifiers and print these on relevant packs of medicines it produces, as a 2D data matrix and (space permitting) in human readable form. All the unique identifiers for a batch of product

will be uploaded by the manufacturer to the European Hub when the product is released for sale. The UIs will then have an "active" status.

The European Hub will validate the UI data and transfer it to the relevant National Medicines Verification Systems. Pharmaceutical wholesalers, community and hospital pharmacies, dispensing medical practices and any other persons "authorised to supply medicines to the public" will connect to their local NMVS.

As part of the dispensing process, pharmacies will scan the UI and send the details to the NMVS, which will compare the UI with the data uploaded by manufacturers; this process is known as verification. If the two items match, a confirmation message will be returned. The dispenser will then send another message to the NMVS to change the status of the product to "Inactive – decommissioned", preventing any other pack with the same UI from being authenticated – duplication of packs being a sign that falsification might have occurred. This process is known as decommissioning. During dispensing, there will also be a check that the pack still has an intact anti-tampering device. The FMD system can also be set to stop the dispensing of products that have been withdrawn, recalled or which are known to be stolen.

Parallel traders will also be able to use the system. They will decommission the UIs of products to be repacked or relabelled and then upload new UIs (maintaining a link at batch level to the original product **[4]**.

The FMD work flow process is represented as the **Figure 2** shown below.

REQUIREMENT OF FMD

• The FMD specifies that all unit-of-sale prescription medication packs (with probable exceptions for considered low-risk products) bear a "safety feature" consisting of a Data Matrix code and readable human data, and must be tamper- evident.

A minimum of four pieces of information must be used in the code:

- batch number,
- expiry date,
- global trade object number (GTIN) and
- A randomized serial number.

A fifth data string for national usage is printed by certain countries. The details must also be written, printed next to the code, in human readable form. Manufacturers (and registered parallel traders) will code and report their products to a central EU hub managed by the European Medicines verification organisation (EMVO).This will push data down to appropriate national data repositories run by corresponding National

Medicines Verification Organisations (NMVOs). Pharmacists (or other authorized persons) will scan the codes during the dispensing process and these codes will be checked against those local databases. **[5]**.

FMD: SAFETY FEATURES

The Falsified Medicines Directive was a legislation adopted by the Parliament of the European Union aimed at improving the safety of the manufacture and delivery of medicinal products in Europe and at protecting patients from falsified medicinal products in the legal supply chain of pharmaceuticals.

The main safety features adopted are shown in **Figure 3.**

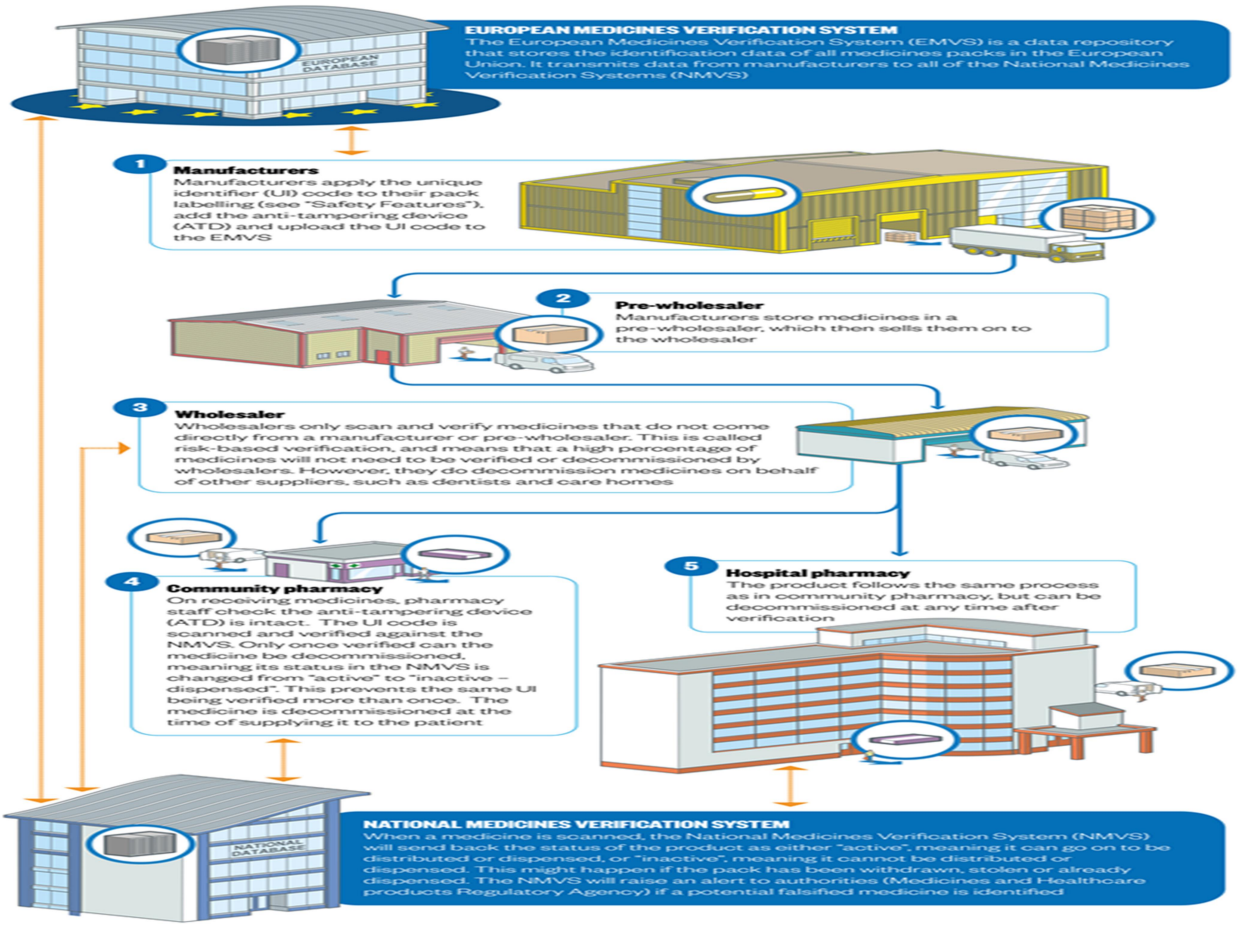


Figure 2: FMD work flow process [4]

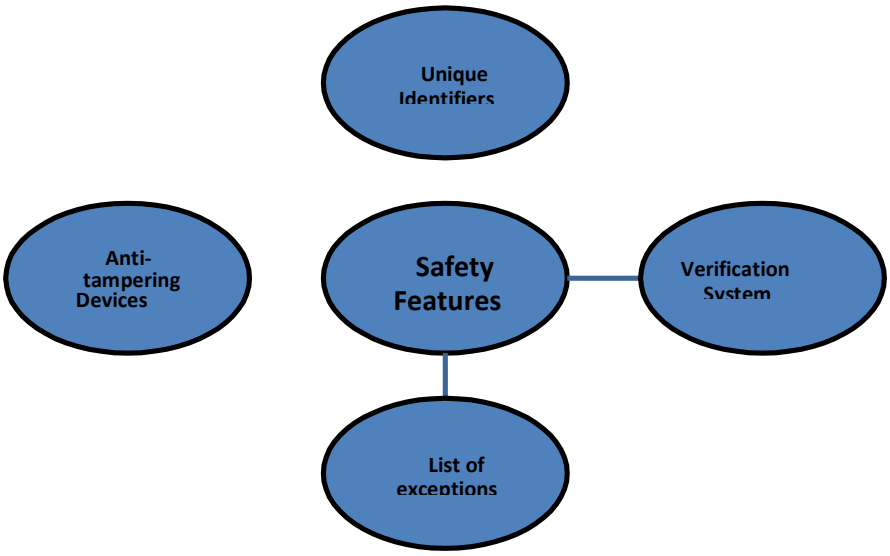


Figure 3: Main safety features developed

The main safety features that have been introduced by the Regulation which stems from the FMD include introduction of alphanumerical code enabling the identification and authentication of individual packs bearing Unique Identifiers (UI); Anti- tampering devices (ATD) that will allow for ascertaining if tampering has taken place; the introduction of repositories systems for the UI to keep a record across EU, as well as formulation of lists of exceptions for bearing or not bearing the safety features.

The UI and the ATDs are expected to be installed on all medicinal products as shown in **Figure 4**. The UI can be alphanumerical code enabling identification and authentication of individual packs. The technical characteristics of a UI include a product code, a serial number and national reimbursement or identification number, a batch number, and an expiry date.The ATDs are meant to verify whether a pack of medicine or product has been opened or tampered with. For example, it could be film wrappers, shrinkable seals, breakable caps, tape seals, blister packs, etc. The main idea is to have such type of packing that if it is tampered with, it would leave audible or visible traces and the consumer or the authorities will be able to detect the problem.

Under the FMD, all new packs of prescription medicines placed on the market in Europe from February 2019 onwards will have to bear two safety features in **Figure 5**.

Figure 4:Examples of Safety Features Developed

Figure 5: FMD pillbox showing safety features

The unique identifier must be carried in a 2D data matrix code. The information contained within this is specified in the Delegated Regulation. The information in the 2D code must also appear on the package in human readable format. Often this will appear where the batch number and expiry date are currently located on the packaging. Sometimes due to the size of the carton it will not be possible to accommodate this information as currently and other solutions will be needed. Exceptionally the information may be split over different faces of the carton.

The human readable information with the 2D data matrix code can appear in any order. Any descriptive terms may be used provided it is clear what is being referred

to. Where necessary the prefix descriptive terms may be located above or adjacent to the information

In addition to having UI and ATDs, an end-to-end verification system is expected to be put in place. It is not a full track & trace system.Essentially, an end-to- end verification system entails the manufacturers or the Market Authorisation Holders (MAH) on one end, and the pharmacies or hospitals that receive the medicinal products, on the receiving end. Firstly, the manufacturers or the MAH are responsible for ensuring that the UIs are printed or applied to the packaging of the medicines and the information regarding the UIs is uploaded in the secure repository system. Secondly, it is also the responsibility of the manufacturer or the MAH to apply the ATDs on the packaging.

In addition to having UIs and ATDs on the medicinal products, the verification system has also been established to further strengthen the protection of the medicinal products. Furthermore, the Regulation provides for the establishment of a Repositories system. The primary responsibility of the repositories system is to store information on the legitimate UIs and facilitate the authentication, verification and decommissioning of UIs at any point of the supply chain. In addition, it would also be the central database, where the detection of potential falsification of pharmaceutical products will come to light. The Member States will be in charge of supervising the repositories system and enforcing the requirements of the delegated Regulation.

In addition to the above, the Regulation on Safety Features also provides for two lists of exceptions. The general rule governing the principle of application of Safety Features is that if it is a prescription medicine, it has to bear the safety features and if it is a non-prescription medicine, it will not bear the safety features. However, there is a possibility of having an exception to these rules, if an assessment shows that there is a considerable risk of falsification. These exceptions are included in Annex I and II of the Regulation 2016/161. Annex I enumerates the list of medicinal product categories that are subject to prescription but do not bear the safety features, referred to in Article 45(1).The prescription medicines exempted from the Safety features are, for example, homeopathic, radiopharmaceuticals, ATMPs, medical gases, certain solutions, contrast media, allergy tests and allergen. In addition, Annex IIenumerates the list of product categories that are not subject to prescription and do not bear the safety features, referred to in the Article 45(2).[5]

TECHNICAL SPECIFICATIONS OF THE UNIQUE IDENTIFIER

Composition of the unique identifier

The manufacturer shall place on the packaging of a medicinal product a unique identifier which complies with the following technical specifications:

a. The unique identifier shall be a sequence of numeric or alphanumeric characters that is unique to a given pack of a medicinal product.
b. The unique identifier shall consist of the following data elements:
    i. a code allowing the identification of at least the name, the common name, the pharmaceutical form, the strength, the pack size and the pack type of the medicinal product bearing the unique identifier ('product code');
    ii. a numeric or alphanumeric sequence of maximum 20 characters, generated by a deterministic or a non-deterministic randomisation algorithm ('serial number');
    iii. a national reimbursement number or other national number identifying the medicinal product, if required by the Member State where the product is intended to be placed on the market;
    iv. the batch number;
    v. the expiry date.
c. The probability that the serial number can be guessed shall be negligible and in any case lower than one in ten thousand.
d. The character sequence resulting from the combination of the product code and the serial number shall be unique to a given pack of a medicinal product until at least one year after the expiry date of the pack or five years after the pack has been released for sale or distribution in accordance with Article 51(3) of Directive 2001/83/EC, whichever is the longer period.
e. Where the national reimbursement number or other national number identifying the medicinal product is contained in the product code, it is not required to be repeated within the unique identifier.

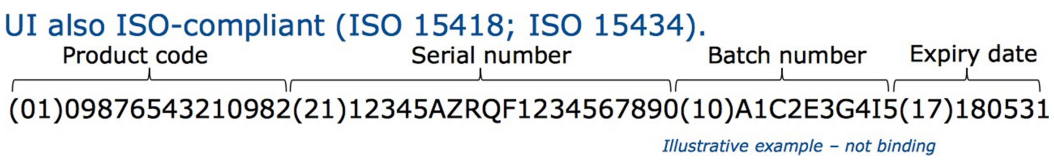


Figure 6: Unique Device Identifier

Carrier of the unique identifier

1. Manufacturers shall encode the unique identifier in a two-dimensional barcode.
2. The barcode shall be a machine-readable Data Matrix and have error detection and correction equivalent to or higher than those of the Data Matrix ECC200. Barcodes conforming to the International Organization for Standardisation/International Electro technical Commission standard ('ISO/IEC') 16022:2006 shall be presumed to fulfil the requirements set out in this paragraph.
3. Manufacturers shall print the barcode on the packaging on a smooth, uniform, low-reflecting surface.
4. When encoded in a Data Matrix, the structure of the unique identifier shall follow an internationally-recognised, standardised data syntax and semantics ('coding scheme') which allows the identification and accurate decoding of each data element of which the unique identifier is composed, using common scanning equipment. The coding scheme shall include data identifiers or application identifiers or other character sequences identifying the beginning and the end of the sequence of each individual data element of the unique identifier and defining the information contained in those data elements. Unique identifiers having a coding scheme conforming to ISO/IEC 15418:2009 shall be presumed to fulfil the requirements set out in this paragraph.
5. When encoded in a Data Matrix as data element of a unique identifier, the product code shall follow a coding scheme and begin with characters specific to the coding scheme used. It shall also contain characters or character sequences identifying the product as a medicinal product. The resulting code shall be less than 50 characters and be globally unique. Product codes which conform to the ISO/IEC 15459-3:2014 and ISO/IEC 15459-4:2014 shall be presumed to fulfil the requirements set out in this paragraph.

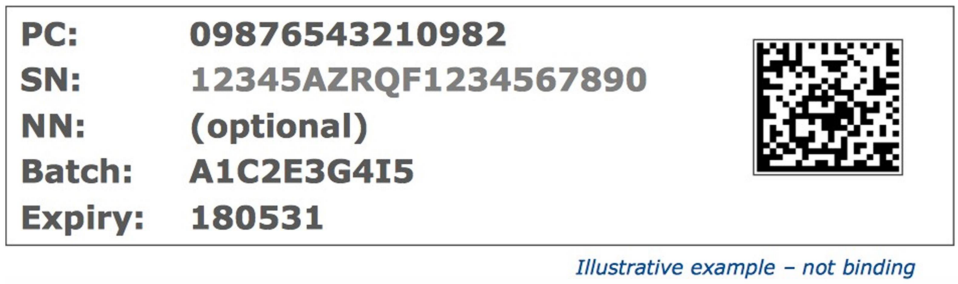


Figure 7: 2d Barcode Matrix

Quality of the printing of the two-dimensional barcode

1. Manufacturers shall evaluate the quality of the printing of the Data Matrix by assessing at least the following Data Matrix parameters:
   i. the contrast between the light and dark parts;
   ii. the uniformity of the reflectance of the light and dark parts;
   iii. the axial non-uniformity;
   iv. the grid non-uniformity;
   v. the unused error correction;
   vi. the fixed pattern damage;
   vii. the capacity of the reference decode algorithm to decode the Data Matrix.
2. Manufacturers shall identify the minimum quality of the printing which ensures the accurate readability of the Data Matrix throughout the supply chain until at least one year after the expiry date of the pack or five years after the pack has been released for sale or distribution in accordance with Article 51(3) of Directive 2001/83/EC, whichever is the longer period.
3. When printing the Data Matrix, manufacturers shall not use a quality of the printing lower than the minimum quality referred to in paragraph 2.
4. A quality of printing rated at least 1,5 in accordance with ISO/IEC 15415:2011 shall be presumed to fulfil the requirements set out in this Article **[6]**.

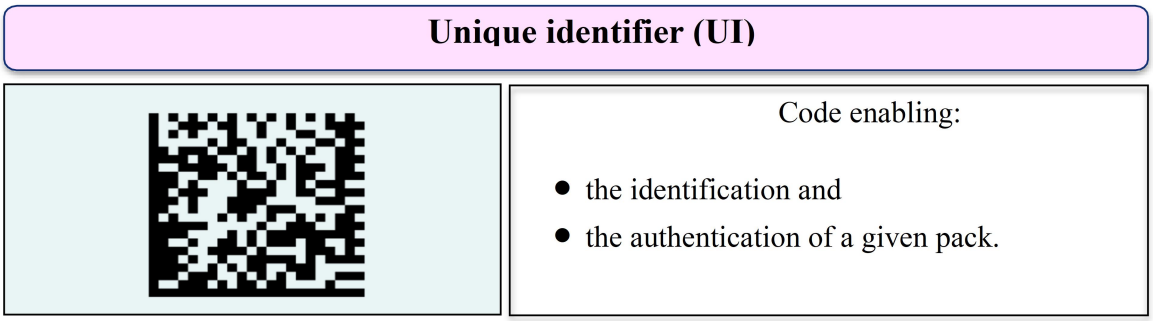
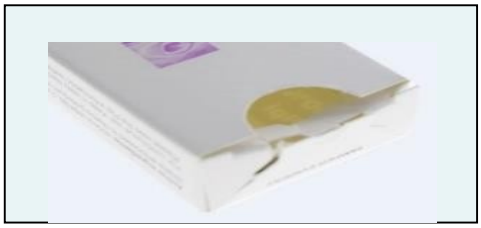


Figure 8: Unique Identifier

Anti-tampering device (ATD)



Device allowing the verification of whether a pack has been opened/tampered with.

Figure 9: Anti Tampering Device

Where should be the UI incorporated

The manufacturers will print the barcode on all packaging of medicines subject to prescription ona smooth, uniform and very reflective platform, which at the same time will identify individually each of these to ensure patient safety. The identification and verification of packaging involves the creation, management and access to the repositories system, a central information and data router (hub) and a national or supranational repositories connected to the hub, which will store the information on the identification of the packaging unit. Each country has its own repository system.

We must be able to identify and verify the authenticity of each package of medication all the time that is on the market, plus the additional time required for the return and disposal of the packaging after its expiry. Therefore, the character sequence resulting from the combination of the product code and serial number must be unique for each package of a medicine until at least one year after the drug has been released or distributed. If we want the probability to be remote for the falsifiers to find out a serial number, it will be generated according to specific rules of randomization. The UI must be encoded using a standard syntax and structure data so that it can be decoded and recognized throughout the whole Union through a common scanner.

However, all codes will be stored in a system of repositories, which will be connected to NODOFARMA at the same time. Nodofarma, is a database system that facilitates the digital transformation of the sector. It contains a private cloud, in an environment dedicated to pharmaceutical services, high levels of security, confidentiality, availability and integrity of transactions and data as well as audit trails throughout the chain. Furthermore, manufacturers must keep records of transactions on the unique identifier of a drug after its deactivation system repositories for at least one year after the expiry date or until five years after the container has been sold or distributed.

Figure 10: Simulation of container with data matrix for unit verification

Human-readable format

Manufacturers shall print the following data elements of the unique identifier on the packaging in human-readable format:

(a) the product code;

(b) the serial number;

(c) the national reimbursement number or other national number identifying the medicinal product, if required by the Member State where the product is intended to be placed on the market and not printed elsewhere on the packaging **[7]**.

CONCLUSION

The falsification of medicines is a significant concern globally, impacting all nations in numerous ways. In addition to addressing the issue of counterfeit medications, it is essential to ensure that people do not lose confidence in the benefits of pharmaceuticals and do not stick to their therapies. Consumer sales of falsified medicines have risen dramatically due to the proliferation of the Internet and the challenge of monitoring drug suppliers on the Internet. Certainly, international and local harmonization with regard to the concept and coordination of counterfeit medicines is required to ensure effective enforcement, monitoring and research. The probability of spurious drug use is proportional to the number of illicit drugs sold. The cause of the illness is exceedingly difficult to identify if there is doubt that a counterfeit drug has been consumed. The primary benefit of the serialization approach is to provide drugs with improved protection so that they meet patients in an integral way, ensuring that laboratories manage to supply and comply with regulatory requirements.

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