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# New regulations regarding falsified medicines in Romania

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**Abstract**. One of the most important aspects of a medicinal product is represented by its quality assurance, which makes it safe and reliable to use. Unfortunately, in recent years, the counterfeit medicine industry has been growing steadily, which has necessitated the introduction of new regulations and methods to control the quality of medicines. In the first part of the study, the counterfeit product has been described and the methods by which it can be brought to market, with the development of the online environment being one of the main reasons for the growth of this illegal industry. The study continues with some examples of counterfeit pharmaceuticals and how they can be recognized by health professionals, and then the impact of these drugs on society today is presented. Finally, some ways to combat this phenomenon were presented, with an emphasis on the introduction of the serialization of medicines, a very important directive implemented by the OSMR. Counterfeiting of medicines is a global problem, and there is a need for increased and effective international coordination and cooperation to ensure the effectiveness of anti-counterfeiting strategies, particularly in relation to the sale of such products on the Internet. To this end, the Commission and the Member States should cooperate closely and support the ongoing work of international forums on this issue, such as the Council of Europe, Europol, and the UN.

**Keywords**. counterfeit medicine, new regulations, OSMR, serialisation, cooperation

## 1. Introduction

One of the essential criteria for a medicine is to ensure its quality, along with its efficacy and safety. The existence of falsified medicinal products on the pharmaceutical market and their use by patients threatens to undermine progress toward the Sustainable Development Goals [1]. Such products may be of poor quality, unsafe, or ineffective, affecting the health of those who take them [1]. Increasing levels of demand for medicines, vaccines, and various other medicinal products in most countries, in addition to poor supply chain management and the growth of e-commerce, also create new opportunities for the introduction of falsified medicines into the supply chain.

Unfortunately, reliable information on the true public health and socio-economic impact of falsified medicines is scarce. A stronger evidence base is needed to prevent, detect, and respond to counterfeit products and the public health threat that they pose [2].

Between 2014 and 2015, the Pharmaceutical Safety Institute (PSI) recorded a 34% increase in such incidents of falsified medicines. Although certain regions and countries, such as Asia, Latin America, and China, are considered to be the most common sources of counterfeit medicines, they pose a threat to all countries.

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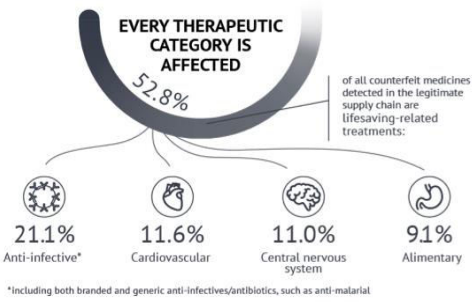
Once counterfeit medicines enter the supply chain, they endanger the lives of patients across the globe, including in high-income countries, and this international threat is magnified by the online market for counterfeit medicines [3]. In 2012, WHO stated that the counterfeit medicine industry is worth approximately $431 billion per year, other estimates have not been reported in recent years due to the rapid growth and spread of this practice in the industry [4]. Authorities are finding it difficult to curb counterfeit medicines due to a lack of control and governance over the Internet [4].

Every category of medicine can be affected by falsification, regardless of whether a medicine is an innovative product or a generic medicine (Figure 1).

**Figure 1.** Main categories of medicines affected by falsification [5]




## 2. What is a counterfeit medicine?

Counterfeit medicines are medicines that do not respect intellectual property rights and/or infringe trademark laws. Another important and dangerous method is the marketing of pharmaceutical products with higher or lower amounts of active substances [6]. Counterfeit medicine is any medicine for which a false presentation is made:

- identity, including packaging and labeling, name, or composition in respect to any of its ingredients, including the excipients and strength of those ingredients;
- source, including manufacturer, country of manufacture, country of origin, and marketing authorization holder;
- history, including records and documents relating to the distribution channels used [7].

Figures 2-4 show the differences between genuine and counterfeit medicines.

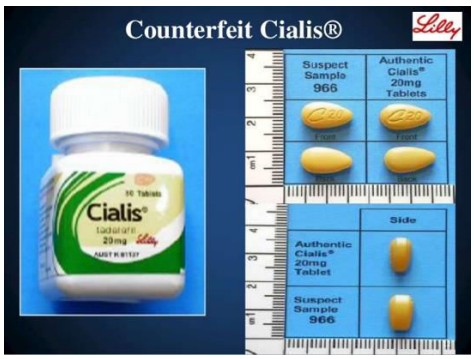



**Figure 2.** Comparison between original and counterfeit Cialis


**Figure 3.** Comparison between the original Coartem product and the counterfeit one

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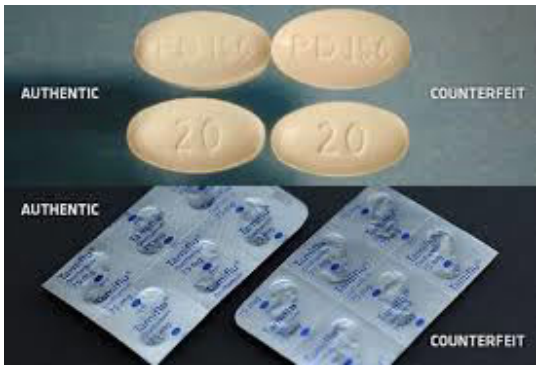


**Figure 4.** Comparison between the original Tamiflu and the counterfeit produc

## 3. The impact of counterfeit medicines on society

Figure 5 shows the impact of falsified medicines on public health and socio-economic factors.

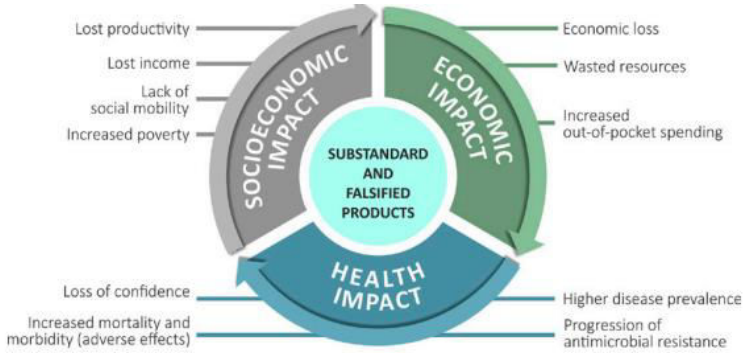


**Figure 5.** The impact of counterfeit medicines on the public and economic sectors

**Mortality and morbidity**

Any product containing a hazardous contaminant (including dangerous or high levels of the active pharmaceutical ingredient) will present an immediate hazard to the individual who will administer it. Patients may also die, or their condition may be prolonged or worsened, if their condition is not treated because the "medicine" they are administering does not contain the active substance or is at a subtherapeutic concentration [8].

**Disease prevalence**

When infectious diseases are not prevented, cured, or controlled because prophylactic products are falsified, the prevalence of the disease is likely to increase. In today's globalized world, where microbes travel long distances with human hosts, this implies a rapid spread of disease to non-endemic regions. An antimalarial or emergency contraceptive, for example, that looks visually identical to the licensed product but is composed of potato or cornstarch, may not cause a toxic reaction but will fail to treat malaria [8].

**Antimicrobial resistance**

It is partly caused by pathogens exposed to subtherapeutic doses, which may be due to the administration of spurious antimicrobial drugs. In many cases, levels of the active substance are so low or nonexistent that treatment will be ineffective.

**Loss of trust**

Counterfeit medicines can contribute to an erosion of trust if patients develop a suspicion or distrust of health professionals, the health system, and even other public institutions. If doubts about the quality of medicines cause people to stay away from certain health facilities,

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refuse vaccination for their children, or fail to take treatment as prescribed, their health may suffer [2].

## 4. Measures to combat counterfeiting

To combat the risk of falsified medicines, the European Parliament and the European Council have adopted a Falsified Medicines Directive (FMD), which aims to improve patient safety by mandating manufacturing authorization holders to implement a system to prevent falsified medicines from entering the legal supply chain [9].

In practice, pharmaceutical manufacturers will have to apply a unique identifier (i.e. a serialization number) to the outer package of medicines [10]. Serialization of medicines is a practice that provides a unique recognition number for each unit of medicine. The given number can be used for product traceability and authentication in the distribution chain, allowing the identification of counterfeits [10].

There are several essential elements to be entered in a serial number: a product code capable of providing essential characteristics such as name, pharmaceutical form, strength, packaging, batch number, expiry date, and a serial number, the latter being obtained by a computer algorithm [10]. As of February 2019, this European Medicines Verification System (EMVS) ensures that medicines are verified throughout the supply chain and at the time of delivery to the patient (Figure 6).

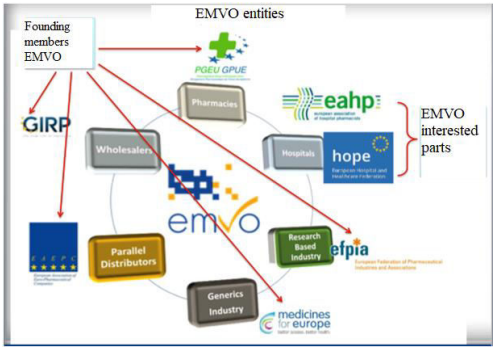


**Figure 6.** EMVO entities [11]

The products included in the scope of Directive 2011/62/EU are all prescription-only products, with a few exceptions specified in the delegated regulation. All manufacturers (national and international) must purchase the appropriate equipment for the production stage of medicinal products to comply with the new rules.

The purpose of counterfeiting and forgery in other areas turns out to be a problem that is driven by price and demand. The same factors have been identified in the health sector. For example, a Pfizer-sponsored study showed that the market for counterfeit medicines in developed countries (which is almost exclusively internet-based) is dominated mainly by so-called "lifestyle" medicines, such as the well-known erectile dysfunction and weight loss products, followed by oncology drugs and cold and flu medicines [4].

In fact, there are very few problems with counterfeit medicines in the legal supply chain. The prevalence of counterfeit medicines in the legal supply chain is estimated at only 0.005%.

Upgrading pharmaceutical packaging lines to apply serialization and verification functions will have a huge financial impact on the generic industry.

There are 10,000 packaging lines working efficiently to supply generic medicines to European patients. Upgrading these lines to apply serialization and verification features costs around €50,000 per packaging line. The lifetime of this new equipment (hardware and

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software) on a packaging line is on average 5 years. Applying safe features adds a cost of €1 billion per year to the manufacture of generic medicines [12].

Every year in Europe, 10 billion packs of generic medicines are distributed; applying safe features to packaging adds €0.10 to the cost of goods per pack of generic medicines.

In their impact assessment, the European Commission acknowledges that the financial impact of this legislation may be most satisfactory for the generic industry and small and medium-sized enterprises [13].

**Serialization in Romania**

The Romanian Organisation for the Serialization of Medicinal Products (OSMR) is a non-governmental, autonomous, independent, apolitical, and non-profit organization (Figure 7), established for the implementation of the European Directive 2011/62/EU on counterfeit medicines and the Commission Delegated Regulation (EU) 2016/161 of October 2, 2015 [13].

The mechanism for the verification and serialization of medicines on the Romanian market has been in place since February 9, 2019 (EU Directive 62/2011) and Delegated Regulation 161/2016, which established specific ways of verifying and securing medicines against counterfeiting, a problem that leads to loss of life and causes damage to health systems worldwide of over 100 billion euros annually [13].

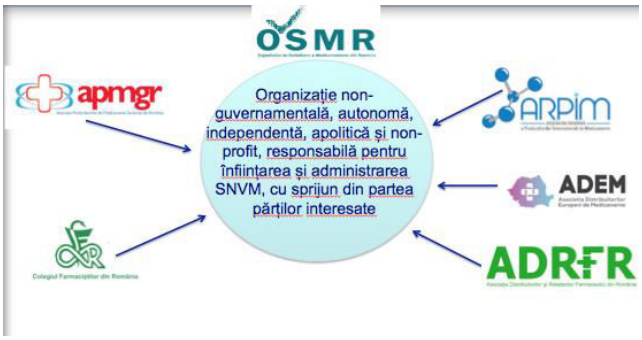


**Figure 7.** Founding members of OSMR [11]

OSMR is responsible for the implementation and administration of the National Drug Verification System (NDVS), a verification platform where pharmacies or other interested parties can verify the authenticity of a product.

There is an alarming increase in the number of medicines detected to be falsified in terms of identity, history, or source in the European Union. They usually contain substandard or falsified ingredients, ingredients in incorrect dosages, or missing ingredients, thus posing a threat to public health [3].

Previous experience indicates that such falsified medicines do not only reach patients through illegal means but also through the legal supply chain. This poses a particular threat to people's health and can lead to patient distrust even in the legal supply chain.

As a result, the European Union has provided, through Directive 2011/62/EU, for the amendment of the Community code relating to medicinal products for human use as regards the prevention of falsified medicinal products from entering the legal supply chain [14]. The Directive requires the introduction of safety features consisting of a unique identifier and a tamper-evident feature on the packaging of certain medicinal products for human use to enable their identification and authentication. By means of Delegated Regulation (EU) 2016/161, the European Commission established a set of detailed rules for safety features appearing on the packaging of medicinal products for human use. As of February 9, 2019,

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only prescription-only medicines carrying the new safety features can be put into circulation [14].

In this respect, additional verification measures need to be taken, from the production stage to the release of the medicinal product to the final user, the patient.

Thus, the manufacturer must ensure the authenticity and quality of the raw materials used, both for the active substances and the excipients used [11]. The manufacturing authorization holder must ensure that good manufacturing practices and good distribution practices are observed by manufacturers and distributors of starting materials. This is done by carrying out audits at the manufacturing and distribution points of these collaborators [11].

The structure and print quality of the two-dimensional barcode containing an identifier must allow very fast reading and reduce reading errors to a minimum in order to facilitate verification of authenticity and the removal of a unique identifier by wholesale distributors and persons authorized or entitled to dispense medicinal products to the public [14].

The data elements of the unique identifier should be printed on the packaging in a human-readable format so as to allow verification of the authenticity of the unique identifier and its removal from use if the two-dimensional bar code cannot be read.

Multiple two-dimensional barcodes on the packaging of medicine should be avoided for identification and authenticity verification purposes. The presence of multiple two-dimensional barcodes on the packaging may lead to confusion as to which barcodes should be read to verify the authenticity and identification of a medicinal product. This can lead to errors in verifying the authenticity of medicines and the unintentional supply of falsified medicines to the population [10].

Verifying the authenticity of a unique identifier is not only extremely important for authenticating a medicine but also informs the person performing the operation if the product is expired, recalled, withdrawn, or reported as stolen. Persons authorized or empowered to supply medicinal products to the public should verify the authenticity and recall of a unique identifier at the time the medicinal product is supplied to the public and therefore access the most up-to-date information on the product and prevent products that are expired, recalled, withdrawn, or reported as stolen from being supplied to the public [10].

Scope:

- prescription medicines with safety features on their packaging with the exception of Table 1 medicines;
- over-the-counter medicines in Table II.

**Table I.** List of prescription medicines or categories of prescription medicines that do not have safety features.

| Name of active substance or product group | Pharmaceutical form | Concentration |
|---|---|---|
| **Homeopathic medicines** | Any | Any |
| **Radionuclide generator** | Any | Any |
| **Radionuclide kits** | Any | Any |
| **Radionuclide precursors** | Any | Any |
| **Advanced therapy medicinal products containing or consisting of tissues or cells** | Any | Any |
| **Medical gases** | Medical gases | Any |
| **Parenteral nutrition solutions with an Anatomical Therapeutic Chemical Code (hereinafter referred to as 'ATC') beginning with B05BA** | Infusible solution | Any |
| **Solutions affecting electrolyte balance with ATC code beginning with B05BB** | Infusible solution | Any |

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| | | |
|---|---|---|
| **Solutions producing osmotic diuresis with ATC code beginning with B05BC** | Infusible solution | Any |
| **Additives for intravenous solutions with ATC code beginning with B05X** | Any | Any |

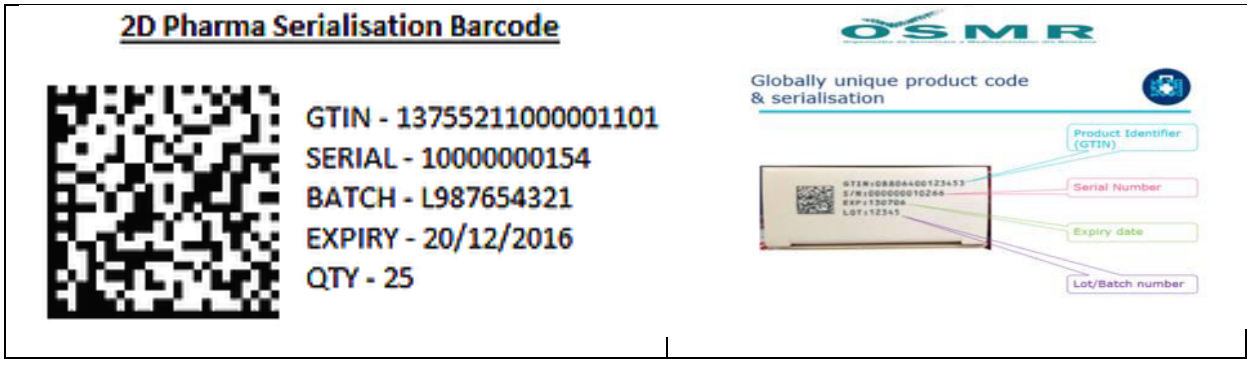
**Table II.** List of medicines or categories of medicines available without a prescription that have safety features

| Name of the active substance or product group | Pharmaceutical form | Concentration |
|---|---|---|
| **omeprazol** | gastro-resistant capsule | 20mg |
| **omeprazol** | gastro-resistant capsule | 40mg |

**Composition of the unique identifier:**
The manufacturer shall affix to the packaging of a medicinal product a unique identifier that meets the following technical specifications:

- the unique identifier consists of a sequence of numeric or alphanumeric characters that is unique to a particular medicine pack;
- the unique identifier consists of the following data elements (Figure 8):
  - a code identifying at least the name, common name, pharmaceutical form, strength, package size, and package type of the medicinal product showing the unique identifier (hereinafter referred to as 'product code');
  - a numeric or alphanumeric sequence of up to 20 characters generated by a deterministic or non-deterministic randomization algorithm (hereinafter referred to as 'serial number');
  - a national reimbursement number or other national number identifying the medicinal product, if required in the Member State where the product is intended to be placed on the market;
  - batch number;
  - expiration date;
- the probability that the serial number can be guessed must be negligible and, in any case, less than one in ten thousand [10].

Manufacturers encode the unique identifier in a two-dimensional barcode (Figure 9 and Figure 10), printing the barcode on the packaging on a smooth, uniform, low-reflective surface so that it can be read very quickly by the scanner when it is unpacked in the pharmacy. Pharmaceutical companies and parallel importers must also apply an anti-counterfeiting device to the outer packaging of each individual sales pack (Figure 10).
Figure 11 shows an example of an anti-counterfeiting device that helps identify counterfeit pharmaceuticals.



| **Figure 8.** Data code elements | **Figure 9.** Unique identifier |
|---|---|
|  |  |
| **Figure 10.** Unique identifier ID | **Figure 11.** Anti-counterfeiting device |

## 5. Conclusions

Patients have the right to safe and high-quality healthcare. Their health and the availability of high-quality medicines are the most important issues for the pharmaceutical industry.

Counterfeiting of medicines is a global problem, and there is a need for increased and effective international coordination and cooperation to ensure the effectiveness of anti-counterfeiting strategies, particularly in relation to the sale of such products on the Internet. To this end, the Commission and the Member States should cooperate closely and support the ongoing work of international forums on this issue, such as the Council of Europe, Europol, and the UN.

In addition, in close cooperation with the Member States, the Commission should cooperate with the competent authorities of third countries in order to effectively combat the trade in falsified medicinal products globally.

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