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FALSIFIED MEDICINES, VERIFY BEFORE YOU BUY

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Secondary scopes:

Legislation and Deontology
Pharmacy Department,
Pharmaceutical Technology
and Physical Chemistry



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ABSTRACT

Counterfeit medicines are a global public health risk. From February 9th, 2019, the new legislation will regulate the pharmaceutical products for human consumption, which aims to avoid into the supply chain, identity drug counterfeit, background or origin, requiring individual packaging identification of all prescription drugs sold on the Spanish market. The pharmaceutical industry, wholesalers and pharmacy offices should be able to adapt to requirements that are in constant transition. Despite of the existence of the *Delegated Regulation (EU) 2016/161*, which shows the unification of the strategies to follow, the differences remain important enough to detect all illicit products on the market. In this review, it has analyzed the evolution of European legislation and safety devices. The detection of spurious products, regularization and control and their consequences, advice for the patient and the incidence rate, are topics covered in depth in this review. Other aspects, such as the factors that influence the counterfeiting are also reviewed. It is urgently needed, improvements in surveillance, including the detection of breaches of security, collection, analysis and dissemination of data to address the needs of public health to combat the global trade of counterfeit medicines. The main purpose of the current legislation is the safety of the consumer and harmonization within the EU.

RESUMEN

Los medicamentos falsificados representan un riesgo para la salud pública mundial. A partir del 9 de febrero de 2019, la nueva normativa comunitaria regulará los productos farmacéuticos para el consumo humano. Ésta tiene por objetivo, evitar en la cadena de suministro, medicamentos falsificados en su identidad, trayectoria u origen, obligando a la identificación individual de los envases de todos los medicamentos de prescripción vendidos en el mercado español. La industria farmacéutica, mayoristas y oficinas de farmacia deben ser capaces de adaptarse a unos requisitos que se encuentran en constante transición. A pesar de la existencia del *Reglamento Delegado (UE) 2016/161*, que muestra la unificación de las estrategias a seguir, las diferencias siguen siendo lo suficientemente importantes como para detectar todos los productos ilícitos en el mercado. En esta revisión, se ha analizado la evolución de la legislación Europea entorno a los medicamentos falsificados, y luego se ha establecido disposiciones detalladas relativas a los dispositivos de seguridad. La detección de productos espurios, la regularización, control y sus consecuencias, consejos para el paciente y el índice de incidencia, son los temas tratados en profundidad en el trabajo. También se repasan otros aspectos como los factores que influyen en la falsificación. Se precisan urgentemente mejoras en la vigilancia, incluida la detección de infracciones de seguridad, recopilación, análisis y difusión de datos para abordar las necesidades de salud pública con el fin de combatir el comercio mundial de medicamentos falsificados. La finalidad principal de la legislación actual es garantizar la seguridad del consumidor y la armonización dentro de la UE.

ABREVIATIONS

SSFFC: Substandard, Spurious, falsely labelled, Falsified and Counterfeit Medical Products.

TAC: Holder of the authorization of commercialization of laboratory.

API: Active pharmaceutical ingredients.

UI: Unique Identifier.

ATD: Anti-Tampering Device.

GTIN: Global Trade Item Number.

SEVEM: Sistema Español de Verificación de Medicamentos.

IMPACT: International Medical Products Anti-Counterfeiting Taskforce.

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios.

AECOC: Asociación Española de Codificación Comercial.

PSI: Pharmaceutical Security Institute.

WHO: World Health Organization.

EMVO: European Medicines Verification Organization.

EFPIA: European Pharmaceutical Industry Associations.

PGEU: Pharmaceutical Group of the European Union.

GIRP: European Healthcare Distribution Association.

EAEPC for parallel trade: European Association of Euro-Pharmaceutical Companies.

OBP: On Boarding Partner, is the contracting party of EMVO and concludes the non-disclosure agreement and participation agreement.

AESEG: Asociación Española de medicamentos genéricos.

1. INTEGRATION OF THE DIFFERENT SCOPES

This review includes three different fields of study, but all are closely related. The new *Delegated Regulation (EU) 2016/161* raises a series of new aspects that pharmaceutical companies have to take into account to put in the market, the products that more index of falsification have. Throughout the essay, it is a question of defining the capacities and competences of each sector and how the new applications are interpreted, derived from the Regulation. It is essential that the entire supply chain work hand-in-hand with all areas of the pharmaceutical industry, either with wholesalers or with customs authorities to have greater control of illegal traffic. It is of little use if the laws are known and not applied correctly. This is the reason why the main scope of my project is **Legislation and Deontology**.

However, there is a substantive issue throughout the review that relates to the area of **Public Health**, since the purpose of the new regulation is to avoid repercussions on the well-being of people from ingesting spurious medicines. After all, the direct application of the analysis of these laws, correlates perfectly with the statistics of incidence and prevalence shown. The original medicines have to follow a study, in order to find, notify and withdraw from the market, counterfeit medicines. In conclusion, this review reflects the impact that has caused this issue raising awareness and increasing precaution of everything that is bought.

And last but not least, it is the field of **Pharmaceutical Technology**, included as a present theme in several parts of the review. The counterfeit medicines regulation contains various measures to improve controls in the manufacture and distribution of medicines. Good practices for distribution, and new drug verification systems, such as the repositories system and safety devices, are incorporated.

2. INTRODUCTION

2.1. HISTORY OF COUNTERFEITING

Concern over the quality of medicines is as old as the drugs themselves. It was first approached at the international level in 1985 at the Conference on **Rational Use of Medicines** in Nairobi. The meeting recommended that WHO, together with other international and non-governmental organizations, should consider establishing a focal point to collect data and inform Governments about the nature and extent of counterfeiting. In 1988, the World Health Assembly requested to undertake programs for the prevention and detection of the export, import and smuggling of unduly labeled, adulterated or non-compliant pharmaceutical preparations.(1)

Although WHO has been working on this complex and politically sensitive issue since the **World Health Assembly**, law enforcement activities intensified in 2006 when **IMPACT** was established, which is composed of international organizations, law enforcement agencies, the pharmaceutical industry and non-governmental organizations.(2)

The subject reached an international level in 2013 at the **MEDICRIME Convention**, held in Madrid as a legal framework for national and international cooperation between health authorities, the police and customs officials in the fight against counterfeit products, including medicines. A total of 23 countries, including Spain, are adhering to this initiative.(3)

The entity that leads the fight against counterfeit medicines at the national level is the AEMPS, which has developed in recent years different information campaigns to raise awareness of the population risks, of the acquisition through illegal drug websites. In addition, the AEMPS is

working on a proposal for the crimes related to illegal drug trafficking to be included in the Criminal Code in the framework of crimes against Public Health, due to the risks associated with the health of patients. (2)

In recent years, people without any concern, are exposed to the intake of dangerous substances, in some cases potentially lethal. This irrational and misguided attitude comes from a mistrust in official medicines.

2.2. THE CONCEPT OF COUNTERFEIT MEDICINES

At an international level, the most common terms are spurious, substandard, falsely-labelled, falsified, counterfeit medicines. It has become important to separate these different categories for the purposes of analysis and identifying strategies to address each issue.(4)

A counterfeit medicine is a product deliberately and fraudulently mislabeled as to its identity or source. Counterfeiting affects both branded and generic products. Counterfeit medicines may include products with the correct ingredients but fake packaging, with the wrong ingredients, without active ingredients or with insufficient active ingredients. They range from random mixtures of harmful toxic substances to inactive, ineffective preparations. Some contain a declared, active ingredient and look so similar to the genuine product that they deceive health professionals as well as patients. But in every case, the source of a counterfeit medicine is **unknown** and its content **unreliable**.(5)

Illegal drugs: are those that, even being original, are acquired through illicit distribution channels or sales. That do not guarantee that its manufacture or conservation is correct or that they have not been manipulated or that they come from channels where their sale is not allowed, for example, internet in the case of prescription drugs or web pages of pharmacies (In the case of over-the-counter drugs).(2)

On the other hand, substandard medicines, also called out of specification, are genuine medicines produced by manufacturers authorized by the National Medicines Regulatory Authority which composition and ingredients do not meet the quality scientific specifications set for them by National standards, and which are consequently ineffective and often dangerous to the patient. Substandard products may be due to negligence, human error, insufficient human and financial resources or falsification.(4)

The absence of universally accepted definition not only makes the exchange of information between countries very difficult, but also limits the ability to understand the true magnitude of the problem at the global level. In the document, the terms spurious medicines and counterfeit medicines are considered as interchangeable.

3. AIMS

The objective of this review is to identify European emerging verification systems designed to ensure the integrity of the global supply chain of original medicines by combating counterfeit drugs. We conducted this review to better understand how current law can act as a unifying framework for different international actions to address a decades-long public health problem that calls for innovative solutions to protect patients around the world.

This review includes interventions such as advice on prevention, detection and advocacy on how to fight and minimize this threat with the interest of increasing knowledge as well as

changing behaviors. It is imperative that allegedly counterfeit products are removed effectively and quickly from distribution channels. In order to facilitate the work of the inspector, it is necessary the collaboration of capable and experienced organizations who participate in the distribution of the products in a preventive way to help identify such products. The current legislation aim is to ensure consumer safety and to allow the functioning of the chain of supplies of original drugs within the EU.

The review is focused on policies related to interventions in public health and public education/awareness, regulatory measures, and some tips to avoid the intake of counterfeit medicines. However, another goal is to describe the new anti-counterfeiting technologies and their future implementation in 2019. The economic impact that the regulation will entail and its timetable for compliance. Other objectives are to analyze the market, influencing factors, the consequences and effects of the counterfeit medicines at European and Spanish level to reflect the magnitude of the dilemma and see their solutions as the national strategy to follow or to timely detect counterfeiting. We will not focus on counterfeit medicines purchased online because it is very extensive. However, it has been used results of Pfizer aiming to represent data with some graphs, on the current situation of the scope of the problem.

Eventually, the last aim of the review is to conduct an interview with a specialist on the issue such as Mónica Soler of AECOC to delve into the Data Matrix code and the characteristics of anti-tampering devices to clarify nuances of the functioning of the verification system as well as to have a deep insight of the changes implementation in the packaging.

4. MATERIALS AND METHODS

The essay methodology consists of an assessment of the current situation through a review of the legislation. The review focuses specifically on emerging technology, on surveys about the relevance of the dilemma, the strategies to follow to implement the changes in the new legislation, and updates/supplementary information. An exhaustive bibliographical search was made, from February 2017 to May 2017, of the main news in the counterfeit world. This search included the full revision of the *Delegated Regulation (EU) 2016/161*. As well as reports from government agencies, media reports (non-scientific sources), corporate websites, press releases, non-governmental organization information or supply chain companies and webs of government and regulatory agencies.

The material is based on a search for online databases, including EUR-Lex-UE using the keywords "counterfeit drugs", "adulterated drugs" and "false drugs". A search was also made of Pharmaceutical companies to obtain graphs. Furthermore, AEMPS and WHO websites were reviewed for additional information. In order to expand the search, it has also been used structured natural language searches with a similar combination of keywords in the popular Google search engine.

After the initial search results, inclusion criteria are applied filtering the results by reviewing abstracts of the articles extracted on the discussion of guidelines and/or professional recommendations, issues related to policy, regulation and traditional forms of authentication and packaging serialization.

Finally, I had the opportunity to attend to the congress held this year in Barcelona: INFARMA and contacted managers of SEVEM. I also interviewed one expert on the field, from the Asociación Española de Codificación Comercial, the Health Sector Manager from AECOC GS1

Spain, Mónica Soler, to get her point of view on the verification regulation. She gave me information about the development and validation of alternative methods of verifying an original medicine.

5. RESULTS AND DISCUSSION

5.1. LEGAL FRAMEWORK

Counterfeit medicines pose a borderless risk to the health of patients and health authorities around the world are developing various initiatives to address this problem. In the case of Spain, since the year 2008, through AEMPS four-year strategies have been carried out. This strategy complements the national regulation, derived from the European regulations, against the falsification of medicines allowing an approach that favors the actions of all the sectors involved.(3)

The current situation following **Directive 2011/62/EU** amending **Directive 2001/83/EC** establishing a **Community code** on medicinal products for human use to prevent the entry of falsified medicinal products into the legal supply chain, contain various provisions to protect the legal chain that have been transposed into national legislation and involve a strengthening of the legal supply chain and the sale of medicines on the Internet. This Directive also includes the basic elements for the development of a European system of safety devices, which will allow in the near future the verification of the authenticity and integrity of each container of dispensed medicine.(6) The Directive is at a macro level. International audits, reviews, inspections, sanctions of all forwarding agents, control of medicines over the internet and safety measures. On the other hand, the Delegated Regulation describes in depth the features of this Directive. (Annex)

The system has been developed in **Commission Delegated Regulation (EU) 2016/161 of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council laying down detailed provisions concerning safety devices which are listed on the packaging of medicinal products for human use**, published in the Official Journal on February 9th 2016.(7) The Delegated Regulation describes the what new tools will provide to prevent the entry of counterfeit drugs into the legal supply chain and their detection. Its implementation will require actions by all agents in the supply chain (manufacturing, distribution, dispensing) as well as the competent authorities. The preparation to carry out these new control mechanisms will be performed during the period of validity of the present strategy, for that reason different actions related to the safety devices have been included such as a unique identifier and anti-tampering device to ensure the safety of medicinal products. Other new measures include: mandatory safety features on the outer packaging of medicines; A common EU-wide logo for identifying on-line legal pharmacies; Tighter standards on the controls and inspections of producers of active pharmaceutical ingredients and strengthening requirements for wholesale distributors.(8) But this regulation does not provide for technical options for the anti-tampering device. The choice of the most appropriated device is left to the manufacturer. (Annex)

5.2. THE COUNTERFEIT MEDICINES MARKET AND ITS ROUTE

According to the WHO it is difficult to define the circuit or route of these drugs. Sources of information include reports from national drug regulatory and compliance agencies, pharmaceutical companies and non-governmental organizations, which generate data on specific geographic areas or therapeutic groups.(9)

In most industrialized countries, there are effective market regulation and control systems, whereby counterfeits have an incidence of less than 1% of market value. On the other hand, it is indicated that in USA the world sales of counterfeit drugs could exceed USD 75 billion annually with a 90% increase in five years, estimate published by the Center of Medicine in the Public Interest in the States United States of America.(9)

Counterfeiters use varied, flexible and intelligent methods to imitate the products and prevent their detection. They can be imported, smuggled or produced locally by large factories with the latest technology or by smaller operators in small establishments. The enormous difficulty of tracing the origins, the channels of manufacture and their distribution does not allow to easily stop their circulation in the market. These infiltrate the legitimate drug supply chain and also use unlicensed online pharmacies to mix fakes between legal drugs.(9) They change from one day to the next, being out of date by the time the study is published.

The factors that determine this activity are essentially the desire for profit, commercial voracity, high prices, a growing demand for medicines that is registered worldwide and the different definitions of counterfeiting, which in some way hamper legal action, as well as offers through the internet, both brand and generic. The expansion of international trade in pharmaceutical principles and medicines also provides another dimension to the complexity of this problem.(9)

5.3. FACTORS FACILITATING COUNTERFEITING

A variety of factors contribute to the proliferation of counterfeit drugs and cover such broad causes as national drug policies, health coverage or poverty. They need to be accurately identified in order to enable governments to detect counterfeiting problems and introduce effective programs to eradicate counterfeit drugs in national drug distribution channels.(10)

Lack of legislation

When there is little or no legislation covering the proper control of manufacturing and distribution of medicines, counterfeiting is likely to evade legal prosecution.(10)

Absent or weak national drug regulatory authority

A competent national regulatory authority for medicinal products is essential in order to ensure that the quality of locally and imported medicinal products is properly assessed and that local manufacturing establishments are adequately inspected. If not, it can facilitate the emergence of illicit markets with greater promotion and commercialization of these markets. Insufficient human and financial resources for drug control activities could also lead to the inability of the national drug regulatory authority to investigate national distribution channels. National pharmaceutical policies, give priority to economic saving against public health in terms of drug manufacturing. Thus, export becomes more important than the control of good practices.

Specifically, the factors that cause this lack of control are:

- Lack of legal mandate for the licensing/authorization of elaborated, imported medicines.
- Lack of inspection.
- Lack of regulation of active ingredients in bulk, importation, distribution and sale of medicines.
- Ignoring the WHO system for certification of the quality of pharmaceutical products subject to international trade as a prerequisite for authorization/importation of medicines.
- Distribution of products through unlicensed/unauthorized intermediaries.
- Sales of products through unlicensed/unauthorized outlets.(10)

Lack of enforcement of existing legislation

When laws are not envisaged, there is a tendency to perpetrate crimes such as counterfeiting, as fear of arrest and prosecution is minimal. In addition, non-observance of trademark rights may encourage large-scale counterfeiting of medicines.(10)

Weak penal sanctions

Absence of or lenient penal sanctions for violations of drugs legislation. It is one of the factors that affect the progress of this illegal activity. The objectives of the Medicrime Convention are to include in criminal law offenses related to counterfeit medicines.(3)

Corruption and conflicts of interest

Inability to arrest, prosecute and convict those responsible for counterfeiting. Corruption and conflicts of interest affect the efficiency of regulatory authorities. (10)

Transactions involving many intermediaries

When products pass through many intermediaries or paper transactions, especially where controls are lax. In the EU, the freedom of movement of goods includes medicines, as an object of intra-community trade (parallel trade). This legal activity sometimes creates weaknesses in the supply chain.(3)

Demand exceeding supply

Drug counterfeiting is a very lucrative business due to the intense and constant demand for medicines and the low production costs. When demand for drugs outstrips supply, counterfeiting may be encouraged as large profits can be made from the manufacture and distribution of counterfeit products. In some cases, high demand can be generated through the inappropriate use of drugs by consumers. For example, the misuse of steroid-containing creams for bleaching the skin and of steroids for body-building have generated a large international market for counterfeited steroid-containing drugs. These are often distributed through unauthorized channels and/or illicit markets. (10)

High prices

The lack of social security coverage or insufficient coverage in countries that do not regulate prices, leads patients to seek the best prices and causes fierce competition among sellers, while providing opportunities for counterfeiters because they can offer more affordable prices. Therefore, when there are important margins between prices, the incentive to supply cheaper counterfeit drugs is greater.(10)

Sophistication in clandestine drug manufacture

The advent of complex equipment for the manufacture and packaging of medicines further complicates the detection of adulterated products because counterfeiters are now able to imitate genuine drugs almost perfectly. The ease of its manufacture being false does not require having large infrastructures or facilities. In fact, most of the counterfeiters arrested to date carried out their activity in ordinary houses, in small domestic factories or simply in the backyard of a house.(10)

Inefficient cooperation between stakeholders

Ineffective controls on the manufacture, importation and distribution of medicines. If cross-sectoral cooperation between regulatory authorities, police services, customs and the judiciary is not working, the chances of escaping detection, arrest and criminal sanctions increase. The responsibilities of each sector should be clearly described. The reluctance of the pharmaceutical industry, wholesalers and retailers to report on counterfeiting to the regulatory authority could prevent national authorities from taking satisfactory measures.(10)

Lack of regulation by exporting countries and within free trade zones

Pharmaceuticals made for export are not regulated by exporting countries according to the same standards as the products processed for consumption in the country. Moreover, they are sometimes exported through free trade zones where drug control is lax and where repackaging and relabeling take place.(10)

It is important to note that there have been no cases of counterfeit medicines that have reached patients in Spain through the legal dispensing channel. However, outside this channel, counterfeit medicines, as well as products adulterated with active ingredients not declared in their composition, are detected.(3)

Lack of social awareness

Illiteracy and poverty, which pose a disadvantage for patients and lack of social awareness of this problem and of measures that emphasize the fight against counterfeiting. (10)

5.4. THE NATIONAL STRATEGY

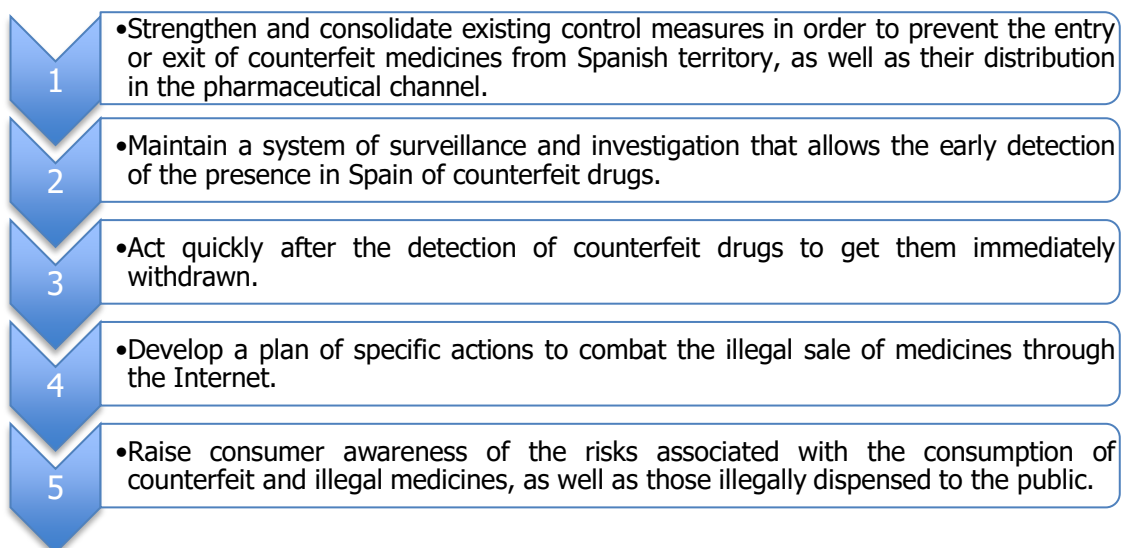
Counterfeiting of medicines is a global problem that affects us all, the traffic of this products generates an activity of 25 times more profitable than selling drugs and if this increase, threatens the marketing of drugs and public health with really worrying numerical figures that estimate the magnitude of 10% of the global pharmaceutical market and in some countries, represent even a 50%, most of these purchased online.(4)

The estimate of deaths due to counterfeit drugs vary from tens of thousands to more than 200,000. Unfortunately, counterfeiters are skillful in copying the packaging and appearance of real drugs. Sometimes you cannot confirm whether a product purchased online is authentic or not until a chemical analysis is made. Modern technology also plays an important role because it is easily accessible and facilitates the manufacturing copies of packaging that are virtually identical to the originals. Counterfeit medicines are difficult to detect, they can escape all controls as a result of increasing globalization and borderless trade as more and more countries manufacture and export medicines, active ingredients and excipients. (4)

In the new actions as well as in those that are maintained, it is necessary to improve on the works developed and always counting on all the agents involved therefore **the strategy to follow is:** (3)

1. Cooperation of all sectors involved, both health and non-health, of a public or private nature.
2. Rapid and ongoing exchange of information between all stakeholders, as well as with health authorities in other countries and with other inter- or supranational bodies.
3. Adequate training of all the agents involved, and increase awareness and awareness of citizens about this problem.

The ultimate aim of all these actions is to protect the health of citizens from the dangers associated with the consumption of counterfeit medicines. In order to achieve this general objective, the following are proposed:(3)



Based on the objectives of the strategy 2016-20019 **sanitary control of pharmaceutical services:**(3)

- Collaboration with other customs officers in the detection of counterfeit drugs in the sanitary controls at the border.
- Regular supervision of drug stores under customs supervision or control by applying inspection
- Criteria based on risk assessment.
- Create and implement specific mechanisms to detect counterfeit drugs in the drug introduced in the European Union through Spain.
- Implementation of controls on imports of active principles laid down in *Directive 2011/62/EU* and evaluate their effectiveness.
- Development of continuing education activities specific to the pharmaceutical inspectors in relation to counterfeit drugs.

In the field of office and pharmacy services:(3)

- Active and regular verification of the legality of suppliers, pharmaceutical laboratories or distribution warehouses with the help of public databases in Europe, AEMPS or regions.
- Notify the competent health authorities of the autonomous community where the offers are located to buy drugs, the suspect related to illegal distribution practices.
- Notification to the competent health authorities of the autonomous community where they are located, any theft of drugs detected.

These checks are also carried out by non-prescription drugs, which include these devices when selling through the website. Therefore, the strategy to follow would be to alert customers with information leaflet when they seek their usual medication and reiterate that they need to take precaution of the drugs for sale without prescription online. There is a shared responsibility by both the distributor for selling the counterfeit medication and also by the pharmacist for performing drug testing before selling it. (3)

We are fortunate that in Europe and in Spain it does not reach 1% and if so has always occurred in channels outside the law. The EMVS contributes to the sustainability and efficiency of the public health systems in the EU.(3)

5.5. DRUG CHECKING AND SAFETY DEVICES SYSTEM

The Counterfeit Medicines Directive is being implemented through a European System for the Verification of Medications (EMVS) managed by an international non-profit organization called EMVO based on serialization packaging through Datamatrix code, to be verified at the point of dispensing. This organization is set up thanks to the agreement of the EFPIA, PGEU, GIRP and parallel trade EAEPC. (11)

The Counterfeit Medicines Directive contains various measures to improve controls in the manufacture and distribution of active ingredients. These measures have required legal changes, elaboration of detailed guidelines (Good practices for the distribution of active substances) and intensive work by the AEMPS, the Autonomous Communities and the Pharmaceutical Inspection Services of the Health and Social Policy of the Peripheral Administration in its execution. (7)

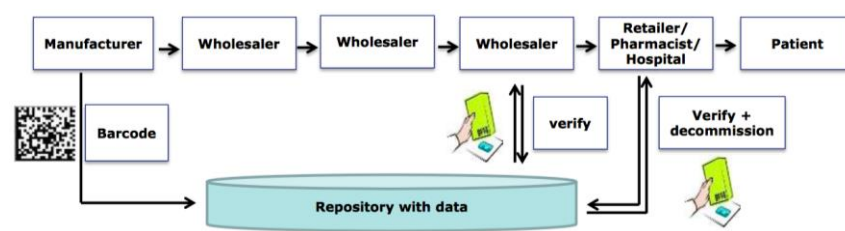


Figure 1: End-to-end verification system + risk based verifications. Adapted from (12)

What is pursued with the drug verification system is to prevent counterfeit drugs in the legal supply chain, with each drug packaging being unique and increasing controls. In this way, it can be verified that we deal with an original container and the organ in charge of developing, executing and managing the system of verification of medicines is the SEVEM.(13)

SEVEM will incorporate a unique identifier to all medications, which will be recorded in a single database, **repositories system** and will be connected to the European Hub, a data router. Its main task is to store the information on the legitimate UIs and allow the verification/decommissioning of UIs at any point of the supply chain. The EU repository, where all data are identified, consists of a central core that will completely connect all national or supranational repositories and it will be established and managed by stakeholders with supervision by competent authorities. The EMVO will manage the European hub. **The information will reside at the European hub; however, the verification will be done in the national repository.** The national EMVO is SEVEM. The role played by the AEMPS is to enter, monitor, but It is not part of society that constitutes the SEVEM nor the EMVO. (13)

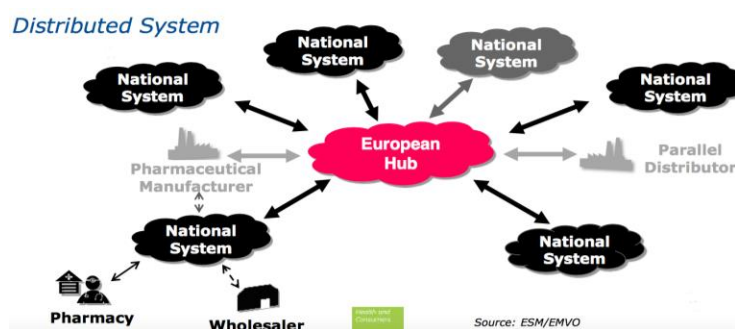


Figure 2: Repositories System Architecture. Adapted from (12)

All prescription drugs, with a few exceptions, and also in some cases those of over-the-counter (OTC), must have the new code and will **mean the disappearance of the traditional precinct code**. When pharmacists receive the product, they must validate it and disable it so that nobody else can sell a product with that code, and will be required to verify that the medication is genuine and has not been manipulated before dispensing. Distributors should also verify the authenticity of the UI and disable the code when the drugs go outside the EU, are expired or have to be destroyed. Generics will also be included in the new system, since they are bound by the rules, but for the price there is not a high risk of counterfeiting.(14)

5.5.1. SAFETY DEVICES IN THE EUROPEAN UNION

Directive 2001/62/EC lays down the types of safety devices and their function, notifications by the authorities to the Commission concerning the medicinal products that will carry them or not, criteria to establish which drugs to take and the extension of the system/use of information by the authorities. (7)

The safety features consist of two elements placed on the packaging of a medicinal product:

1. Verification of the authenticity of individual packs of a drug and its identification through a unique sequence included in a two-dimensional bar code, called Unique Identifier (UI).
2. A device allowing the verification of whether the packaging of the medicinal product has been tampered with anti-tampering device, (ATD).

Medicines authorized in Spain that must be carried by the safety device are all prescription drugs, except those listed in **annex 1, so-called white list**. As well as non-prescription medicines that must carry these devices, listed in **annex 2, so-called black list**. Each country will have its own list. (7) And medicinal products to which Member States have extended the scope of application of the UI or the ATD according to the *Directive 2001/83/EC*.

ANNEX I

List of medicinal products or product categories subject to prescription that shall not bear the safety features, referred to in Article 45(1)

Name of active substance or product category	Pharmaceutical form	Strength	Remarks
Homeopathic medicinal products	Any	Any	
Radionuclide generators	Any	Any	
Kits	Any	Any	
Radionuclide precursors	Any	Any	
Advanced therapy medicinal products which contain or consist of tissues or cells	Any	Any	
Medicinal gases	Medicinal gas	Any	
Solutions for parenteral nutrition having an anatomical therapeutical chemical (ATC) code beginning with B05BA	Solution for infusion	Any	
Solutions affecting the electrolyte balance having an ATC code beginning with B05BB	Solution for infusion	Any	
Solutions producing osmotic diuresis having an ATC code beginning with B05BC	Solution for infusion	Any	
Intravenous solution additives having an ATC code beginning with B05X	Any	Any	
Solvents and diluting agents, including irrigating solutions, having an ATC code beginning with V07AB	Any	Any	
Contrast media having an ATC code beginning with V08	Any	Any	
Tests for allergic diseases having an ATC code beginning with V04CL	Any	Any	
Allergen extracts having an ATC code beginning with V01AA	Any	Any	

Figure 3: List of medicinal products subject to prescription that shall bear the safety features.(7)

ANNEX II

List of medicinal products or product categories not subject to prescription that shall bear the safety features, referred to in Article 45(2)

Name of active substance or product category	Pharmaceutical form	Strength	Remarks
omeprazole	gastro-resistant capsule, hard	20 mg	
omeprazole	gastro-resistant capsule, hard	40 mg	

Figure 4: List of medicinal products not subject to prescription that shall bear the safety features.(7)

Delegated Regulation (EU) 2016/161, applicable since February 9th, 2019, contains the **characteristics of the unique identifier**, which is a numerical sequence, exclusive for each package, which consist of:(7)

- 14 digits **Product code (GTIN)** which identifies the name, common name, dosage form, dose, size and type of container. In Spain, the Directive leaves open several options for the product code, for example how will the GTIN be. The GTIN serves for reimbursement and for identification. It has less than 50 characters and its globally unique, issued by ISO-compliant coding agencies.
- Unique **Serial randomized number**, numeric or alphanumeric sequence of maximum 20 characters generated for a randomized algorithm deterministic or non-deterministic.
- **Expiry date** up to 6 digits (YYMMDD)
- **Batch number** up to 20 alpha-numeric characters
- **National reimbursement number or identification number**, if requested by the State where they go to market.

UI also ISO-compliant (ISO 15418; ISO 15434).


Product code Serial number Batch number Expiry date

(01)09876543210982(21)12345AZRQF1234567890(10)A1C2E3G4I5(17)180531

Illustrative example - not binding

Figure 5: UI model (12)

A part from the UI, it will be added a **Data Matrix Code**, developed in accordance with ISO standards. The two-dimensional bar code can store more information in addition to the data elements of the unique identifier. It is robust, with redundant, repeated information, so if it is damaged at an 80% it could be still read. This residual storage capacity will be used to include more information without putting other barcodes. It is necessary to ensure print quality of the two-dimensional bar code structure in order to minimize errors and read it quickly to facilitate the verification and deactivation of the unique identifier, dispensing of medicines. It must be avoided that the packaging of a drug takes several two-dimensional bar codes for the purpose of verification and identification.(7)

PC:	09876543210982	
SN:	12345AZRQF1234567890	
NN:	(optional)	
Batch:	A1C2E3G4I5	
Expiry:	180531	

Illustrative example - not binding

Figure 6: Data Matrix model (12)

5.5.2. WHERE SHOULD BE INCORPORATED THE UI

The manufacturers will print the barcode on all packaging of medicines subject to prescription on a 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.(7)

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**. (7)

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.(13) 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.(7)



Figure 7: Simulation of container with Data Matrix for unit verification. Adapted from (20)

One of the issues to be resolved is the information that will appear in Datamatrix. The objective is to **eliminate the print of the national reimbursement number** and insert it in the Data Matrix code to prevent duplicate it. Farmaindustria is divided. What is clear is that the information of the national code cannot be lost, due to pharmacovigilance issues or because of the dependence that the computer systems have on the national code. (15) Therefore, there are two possibilities: (Annex)

1. Include directly the national code of each presentation in the Datamatrix, which means **increasing its size** because it must have 5 lines for the industry: Expiration date, batch number, serial number randomized, national code, product code. The drawback is that this

slows down the speed of the production of medicines. The National reimbursement number would not be printed in the packaging, it could be put in the national repository with the link: CN-CP. (Annex)

2. Since the GTIN served for the refund and to identify, the **National code could be transformed in structure of GTIN**, the National reimbursement number would have 14 positions, the same as the GTIN. With the big number of new products coming out, the ranks of the 7 positions for the refund of the national medical product identification are exhausted. However, GTIN is inexhaustible, is global unlike the National number identifying the medical product which is only Spanish. This is the most supported solution. (Annex)

We will have to put in **human reading the GTIN and the serial number** on the packaging. The disparity of authentication mechanisms, due to different national or regional requirements traceability can limit the circulation of medicines in the EU and increase costs for everyone involved along the supply chain. Therefore, it requires applicable regulations and the creation and management system repositories that contain information about the security devices. However anti-tampering devices, such as holograms and glued, can be put on all medications that laboratory want, even in those who are not required by law, while the UI not.(7)

5.5.3. KEY INFORMATION FOR THE PHARMACIST

In a verification system end to end, the **decommission of the unique identifier** in the **repositories system** must be made at the end of the supply chain, **to dispense the medicine**, being the responsibility of the pharmacist to get the information updated and not expired medication reaches the public, recovered, withdrawn or reported as stolen. However, some packages cannot get to dispense. Such is the case, for example of drugs that are to be distributed outside the EU, to be destroyed, the competent authorities have asked as samples or have been returned and cannot resalable inventories.(16)

When making the decommission of the UI in the repositories system, other packaging bearing the same UI cannot be verified.

The pharmacist or persons authorized to dispense medication need to consult the repositories before the check, to verify the authenticity of the UI compared to the genuine UI. It will create an audit trail after the introduction of the UI in the repositories, keeping a complete record of all operations for at least one year after the expiry date of the drug or five years after it has been putted up for sale or distribution. Finally, if everything is correct, the pharmacist will disable it using a common scanner.(16)

If it is unconfirmed that the UI is authentic, the system activates an alarm and the terminal, as a possible incident of forgery, except when the medication longer appears as recovered or removed aimed at its destruction. The effectiveness of the verification system falls off in the subsequent decommission of the UI of each packaging, avoiding that it could be reused by traffickers.(7)

The increased risk of counterfeit medicines must be verified by wholesalers throughout the whole supply chain to minimize the risk of the ones circulating go unnoticed.

5.5.4. THE CHANGE OF STATUS OF A UNIQUE IDENTIFIER DISABLED ENABLED

The action can be performed for manufacturers, wholesalers and authorized persons to dispense drugs such as pharmacists. The change is carried out if:(7)

1. The person making the change has the same authorization and works in the same facilities as the person who cancels the UI.
2. The change takes place no more than 10 days after deactivation.
3. The drug has not expired.
4. The packaging does not appear in the system repositories as recovered, removed, aimed at its destruction or stolen or the person making the change becomes aware of the theft.
5. The drug has been dispensed.

Above all: ensure the decommission of the UI of drugs removed in national repositories; ensure the decommission of the UI of stolen drugs and indicate the reason for deactivation in the repositories (withdrawn, theft...).(16) The pharmacist will require training with all the people involved in the process. The pharmacy must have telephone support to users, systems support all of them in several languages.

5.5.5. MANUFACTURERS, PHARMACEUTICAL INDUSTRY WHOLESALERS AND COMMUNITY PHARMACIES

Manufacturers, wholesalers, and dispensing entities will verify the authenticity of the UI, comparing to the UI of the updated repositories system and the integrity of the ATD. Subsequently, the UI is decommissioned in the repositories system, and if there are no exceptions for the distribution or dispensing of the decommissioned UI, dispensation is continued. Following the sentence of "a chain is as strong as its weakest link", the Commission sees essential that all the users of the system (pharmacies, hospitals and distributors) are identified as authorized to connect to the repository. There will be a record of all transactions.(17)

The first intermediary is the **manufacturers**, which will perform the verification meeting the requirements of the UI; The registration of operations with the UI; Verifications prior to re-labeling; Decommission the UI and, if necessary, reactivating the UI and taking action in case of tampering or alleged falsification.(16) However, to include the safety devices (UI and ATD) must access to the European platform (OBP), resolutions technology supplier, protection of confidentiality of data, and loading codes; Maintain relations with SEVEM with the Operations Committee and make payment of the system which is the implementation and maintenance phase, manufacturers must establish rules.(13)

Second, **the pharmaceutical industry wholesalers**, will have to face costs to adapt the technology to the system. The Software will need to be adapted to carry out risk-based UI checks, at least on returned drugs (by other wholesalers or by dispensing entities); Those received from another wholesaler other than the designated manufacturer or laboratory of the designated drug or wholesaler.(16) Some activities of the distributor are to take measures in case of manipulation or alleged falsification; the decommission of the UI of the system of repositories and if necessary, the reactivation of the same. They should also incorporate **code readers**. What the system offers us is **the disappearance of the coupon seal and an improvement in the management of batches**.(13) Exceptions to the end-to-end system are that some Member States can exempt certain authorized to supply to the public from the verification/decommissioning obligations such as veterinarians, dentists, opticians or paramedics. In this case the verification/decommissioning of the UI is performed by the

wholesaler supplying those persons. What member states cannot do is to exempt pharmacies nor healthcare institutions.(12)

Finally, the **community pharmacies** that will perform the verification of the UI and ATD before dispensing the medications; Decommission the UI and, if necessary, reactivate the UI, as well as take measures in case of manipulation or alleged falsification.(16) The logic of the business for the Pharmacy is to have a double dispensation control by mistake; Verification of drug entry at the pharmacy; Manual verification for reading problems; Multiple verification; A continuity plan: storage of deactivations by network or system drop; Control screen and verification error messages; Integration of verification as the final step of the dispensing process in the electronic prescription. A major investment in computers and equipment should be made to adapt the system and optical readers. However, the COF business provides security for access control, user management and certificates; Governance of the activity in its territory, monitoring of the system at a technical level; Better attention to the collegiate; Prices and their reimbursement.(13)

However, it should be borne in mind that **medicinal products put up for sale or distribution before the date of application** of the measures, February 9th 2019, may **continue to be marketed until their expiry date**.(16)

5.6. COST AND IMPLEMENTATION PATH IN SPAIN

5.6.1. IMPLEMENTATION SCHEDULE AND ROUTE SHEET

The roadmap for the implementation is organized in four phases

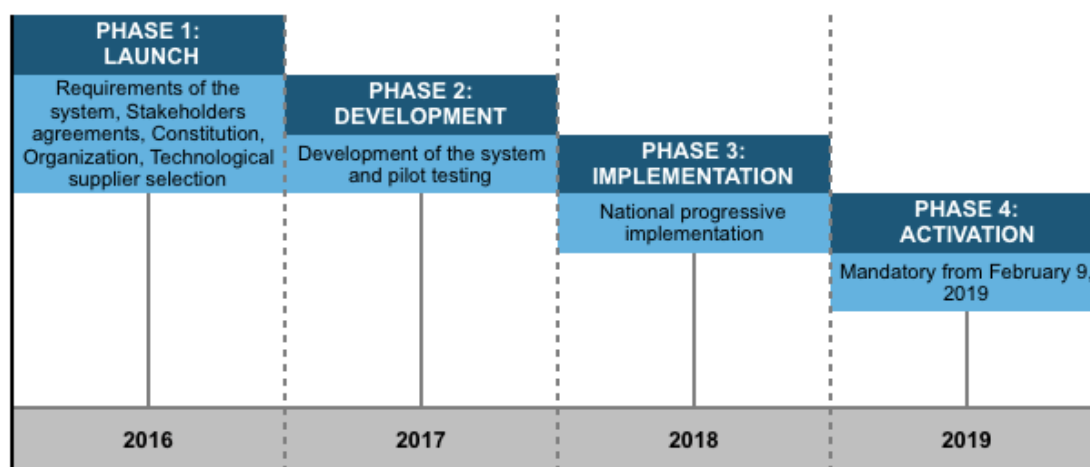


Figure 8: Implementation Schedule of the Verification System. Adapted from(11)

The implementation of the new security system has been planned for SEVEM in four phases, the first being that of **launch**. At the end of the month of June 2016, is the company formed by the different agents and, before year's end, the contracts are awarded to the technology provider. In 2017, the **development phase**, you will begin to pilot testing. 2018, provides for the **gradual implementation** of the project in all the offices of Pharmacy and hospital pharmacy services. The fourth phase, **the activation**, will begin in February, 2019, with the coexistence of prescription and without safety devices **until the year 2024**, when all prescription drugs be incorporated into them.(18)

Talking about the repository system, the development of the European node (EMVO) was completed in 2015 and the first connection to the national node Securpharm was established in July of the same year. It is a large complex system that connects to 150,000 pharmacies, 10,000 distributors, hospitals and other points of dispensing in Europe. In Spain, we are in phase of development of the repository. SEVEM is working on the system and its implementation requirements and is expected to start the phase of piloting with the distribution companies and pharmacies in the month of July 2017.(13)

The program progress is that 16 NMVOs (50%) founded, 4 Contracts signed, the majority of countries progress and aim for Provider Contract in 2017 and countries decide for Blueprint, only 4 remain open. To sum up: 2/3 countries are still behind schedule, still 4 countries did not start Technical work stream and stakeholder alignment is not complete in a few countries (Pharmacies and Wholesalers have not integrated in NMVO set up).(19) It can be seen in the figure below that Spain is in the main stream whereas Germany, Sweden and Finland are perfectly prepared for the change.

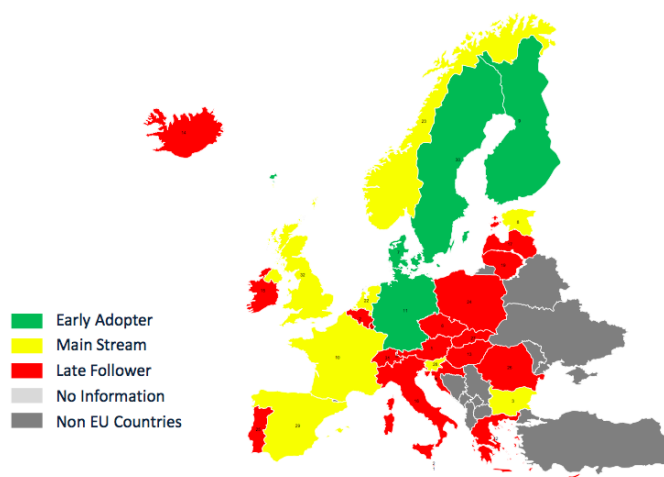


Figure 9: Executive Summary Country Readiness. Adapted from (19)

5.6.2. COST OF IMPLEMENTATION AND MODEL OF FINANCING IN SPAIN

The cost of adapting **production lines** to facilitate unit verification of medicines will reach 200 million euros for companies producing medicines in our country. This figure is based on an estimate made by Farmaindustria taking into account that the unit cost would be between **200,000 and 400,000 euros**. Seals and safety devices must be provided in addition to the serialization of each package. The figure of 200 million is just to adapt the machinery and start working. Subsequently there will be operating expenses, which will be of a permanent nature, for example, the security seals that will have to carry each container. The **cost of each line that must print the Data Matrix and serialize every single packaging** amounts to **300,000 euros**. To this must be added **150,000 euros for technology** to insert in each container the anti-counterfeit seal. It's definitely not a cheap question.(20)

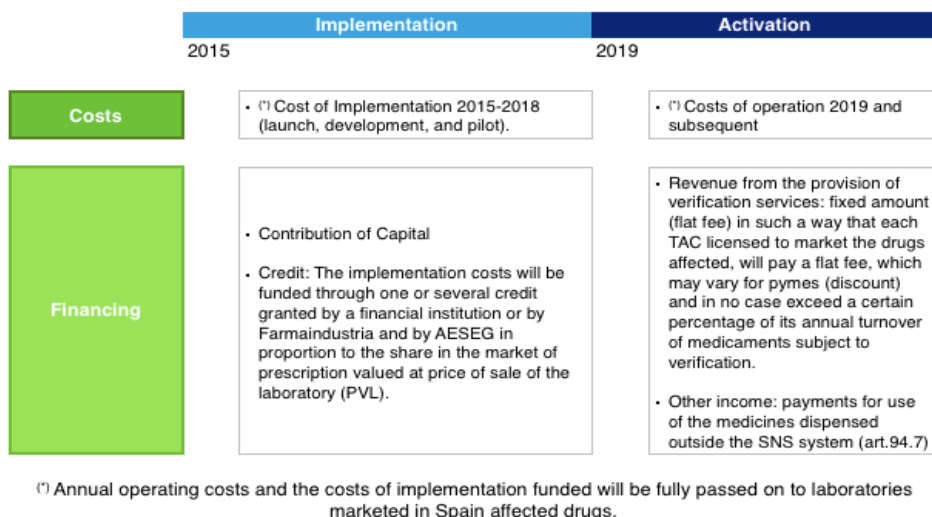


Figure 10: Basic elements of the Spanish funding model. Adapted from(11)

Apart from the costs mentioned that each company will have to assume in its own production plants, there are costs that will be borne by all of them based on a calculation of quota that corresponds to support **SEVEM** and which, according to the estimates made will amount to **5 million euros per year**. The pharmaceutical industry will assume the cost of the start-up and maintenance of the national system and the European node, which Farmaindustria estimates at a cost of between **10 and 13 million euros for launch** between 2016 and 2018 and between **5.5 and 8 million euros from 2019**. To see if the European Commission figures on impact are lower than the industry estimates.(20)

Another cost, although there are still no figures, is the one that will have to assume the offices of pharmacy, the hospitals and the distribution to be able to read Datamatrix codes that will appear in the containers. An investment that will have to be made before February 9th 2019, date on which a drug can only be dispensed in the EU if its authenticity has been verified. Of course, for pharmacies will have the counterpart of being able to end the paper to be able to dispense with the coupon seal for billing to the National Health System.(20)

5.7. THE MAGNITUDE OF THE PROBLEM

In recent years there has been a significant increase in the purchase of counterfeit medicines through non-official channels, such as the internet. It was estimated that in **2010 the sale of fake medicines reached 75,000 million dollars**. Seizures of drugs at the borders of the EU have also increased, from half a million containers in 2005 to more than four million in 2007, which means that **it is multiplied by seven in just two years**.(21)

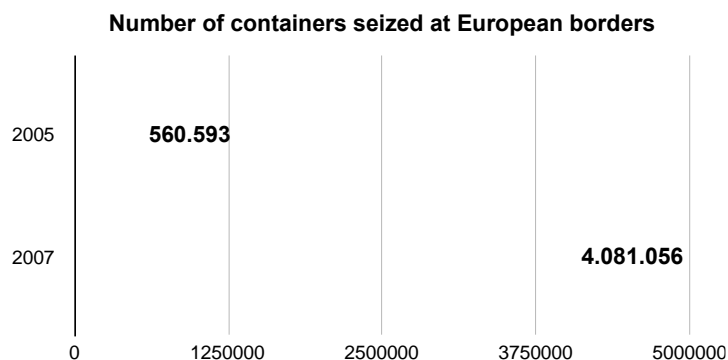


Figure 11: Number of containers seized in Europe

To give an **international overview**, studies conducted by the WHO reveal that one of every ten drugs that are sold in the world are false; a ratio that acquires a 50%, in developing countries. Most industrialized countries with effective regulatory systems and market control (e.g. USA, EU, Australia, Canada, Japan, New Zealand) currently have a very low proportion, less than 1% of market value. However, we must keep in mind that indications point to an increase in the prevalence of spurious medicines even in such countries. Furthermore, many developing countries of Africa, parts of Asia, and parts of Latin America have areas where more than 30% of the medicines on sale can be spurious. Other countries, however, have less than 10%; overall, a reasonable estimate is between 10% and 30%. On the other hand, Soviet republics have a proportion of spurious medicines which is above 20% of market value - this falls into the developing country range. (22)

At least 50% of the medicines purchased online hide their physical address and are false. Also 1% of the medicines sold in developed markets such as the EU, are counterfeit.

PSI has collected data on counterfeiting, illegal diversion and theft incidents for fourteen consecutive years. The yearly totals for the last five years are shown on the adjacent bar chart.

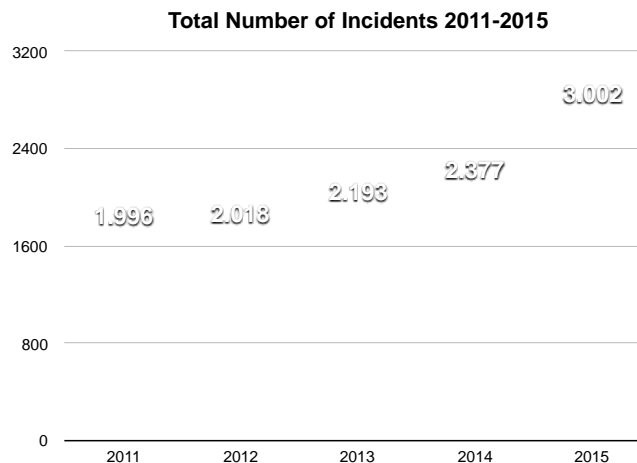


Figure 12: Total number of incidents 2011-2015. Adapted from (23)

PSI has documented 3,002 incidents of pharmaceutical crime during calendar year 2015. From 2011 to 2015 the total number of incidents has increased by 51%. (23)

Counterfeit Seizures 2015

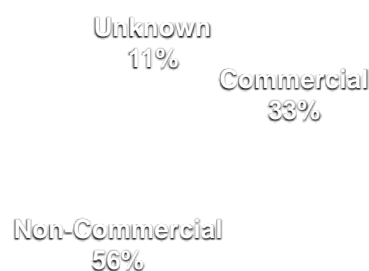


Figure 13: Counterfeit Seizures 2015. (23)

Any incident involving the confiscation of more than 1,000 dosage units is classified as a "commercial" type incident shown in the chart with a 33% increase. Incidents involving less than 1,000 seized dosage units are classified as "non-commercial" which represent 56% of the total seized.(23)

The conclusion is that both commercial and non-commercial seizures increase significantly during 2015. So it is corroborated that small-scale counterfeiting is the most detected by the authorities and possibly the most performed by criminals worldwide.(23) The theft of pharmaceutical products increased by 66%, while incidents of counterfeiting during this period increased by 122% according to the reports of international and professional organizations. However, the true scope of the problem remains unknown.(24)

5.7.1. GEOGRAPHIC DISTRIBUTION

No countries remain untouched by this issue, from North America and Europe through to Sub Saharan Africa, South East Asia, and Latin America. With the exponential increase in internet connectivity those engaged in the manufacture, distribution and supply of SSFFC medical products have gained access to a global market place. A culture of self-diagnosis and self-prescribing has led to the emergence of thousands of unregulated websites providing unsupervised access to SSFFC products. However, it is low- and middle-income countries and those in areas of conflict, or civil unrest, with very weak or non-existent health systems, bear the greatest burden of SSFFC medical products.(4)

To see the geographic distribution of counterfeiting, data is divided into seven regions worldwide, ordered in the contiguous table from which they had the highest number of incidents to which they had less. A total of 3,002 incidents were collected. In all, 128 countries are affected by drug crime. Compared with 2014, PSI recorded a thirty-eight percent increase (38%) in global incidents. In the year 2015, the impact in the Asian region surpassed for the first time one thousand. In North America also increased one hundred percent of the year 2014.(25)

It should be noted that it is not necessarily related the incidence of crimes with the legal absence of some countries. Regions with low incidence, are not exempt from risk of crime. However, every effort is made to effectively identify drug delinquency through inspections and legal action.

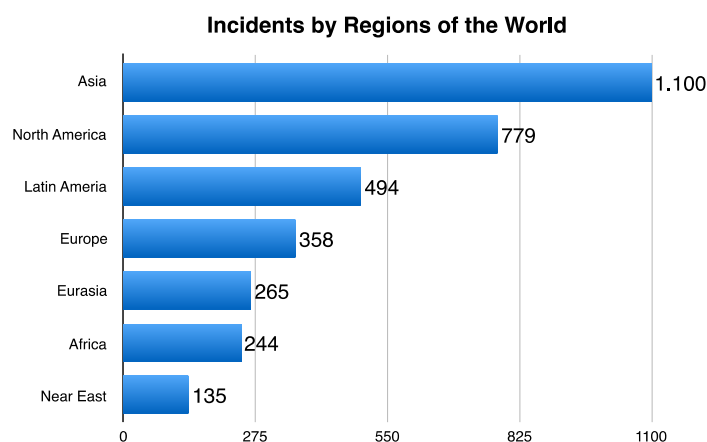


Figure 14: Data collected from incidents of pharmaceutical crime in 2015 by PSI (25)

On the other hand, other unquantified variables impact economically, as the cost to public health that produce side effects due to the use of counterfeit medicines.

5.7.2. ECONOMIC IMPACT

The counterfeiting of medicines is a very lucrative, around 75,000 million dollars. It can be influenced because the law application is different in each region as well as the arrests. Falsifiers do not spend money on GMP, but invest in packaging equipment and the profits are 500 times higher than investments.(19)

The arrests of 1,375 people involved in counterfeiting, diversion or theft of pharmaceutical products worldwide during the year 2015 have been documented by PSI. This figure represents an eight percent (8%) decrease over the total global arrests in the year 2014. It can be concluded that the increase in crime may be due to the decrease in arrests.(26)

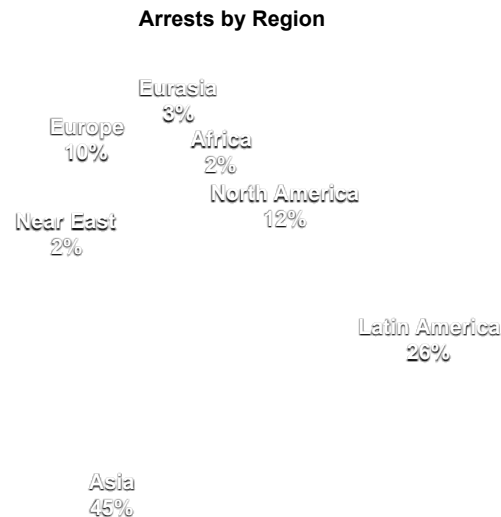


Figure 15: Arrests by Region (26)

An actual case of counterfeiting is what happened to Pfizer in 2010. According to company data, authorities in 53 countries confiscated 8.4 million tablets, capsules and vials of Pfizer counterfeit products, ranging from Norvasc (for hypertension) to Zithromax (antibiotic) and Celebrex (arthritis). Bogus pills sometimes contain chalk, brick dust, paint, and even pesticides. A repugnant batch of pills, originated in China, contained the remains of human fetuses. While companies' resources could be used for research, they have to be used in the fight against adulteration. (27)

The loss of profit on an estimated \$75 billions of counterfeit drug sales is significant. To illustrate the point, assuming that only 50% of the sales of drugs would occur at customary prices, and because counterfeits are most prevalent with the more profitable drugs, **the annual lost commercial profit could be approximately \$18 billion.** (28)

5.7.3. MOST AFFECTED PRODUCTS

The 3,002 incidents that occurred in the year 2015 involved 1,095 different pharmaceutical products. The number of products found in a single incident, ranges from one to thirty-seven different drugs and all falsified by criminal organizations.(26)

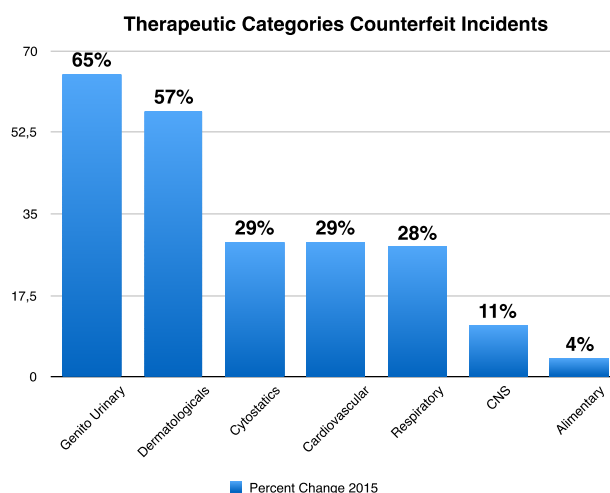


Figure 16: Therapeutic categories. Adapted from (26)

According to the analysis of counterfeit incidents, the therapeutic categories of genito-urinary, anti-infectious and central nervous system (CNS) represent the highest number of incidents. These contain the most falsified medicines. Although the classification of therapeutic categories has not varied much, there has been an increase in the annual percentage. Specifically, the genito-urinary therapeutic category is the one with the largest increase percentage of 65%. Categories with a lower percentage of increase were dermatological 57%, cytostatic 29%, cardiovascular 29%, respiratory 28%, CNS 11% and nutritional 4%.(26)

Generally, the main targets of counterfeiters are medicines used for treating cancer, HIV, malaria, osteoporosis, diabetes, hypertension, cholesterol, cardiovascular disease, obesity, infectious diseases, alzheimer, prostate disease, erectile dysfunction, asthma and fungal infections; antibiotics, anti-psychotic products, steroids, anti-inflammatory tablets, pain killers, cough medicines, hormones, and vitamins; treatments for hair and weight loss.(22) The highest number of reports refer to antibiotics, antiprotozoals, hormones and steroids. In developing countries, the most counterfeit are antibiotics, antiprotozoal drugs and antimalarial drugs whereas in developed countries, hormones and steroids.

According to a study focusing on 8 drug types on the WHO-approved list of drugs, the authors took 899 drug samples from 17 low- and middle-income countries and assessed their visual appearance, disintegration, and analyzed their ingredients by chromatography and spectrometry. The results were that fifteen percent of **the samples failed at least one test considering lower quality drugs**. Also note that the drugs that failed the tests were priced 13-18% lower than non-failing drugs. **So, it was concluded that consumers suspect inferior quality when they pay less**. Furthermore, the study showed that the differential price between failed and non-failing drugs was about 0.59-0.80\$, which could be considerable for developing countries where a large proportion of the population lives on less 1\$ a day. Severe poverty, plus ignorance about the harm of poor quality medicines, supports the decision to purchase counterfeit and substandard drugs. Therefore, poverty is a reason for the selection of lower priced drugs.(22)

This table exemplifies some examples of real cases of counterfeiting.

CATEGORIES (*)	REAL CASES OF COUNTERFET DRUGS
The first case of a counterfeit drug occurred in 1937. An American pharmaceutical company wanted to increase its sales volume. (29)	They used diethyleneglycol (a toxic solvent) to make a sulfanilamide syrup, and more than 100 people, including children.
Inadequate storage can lead to inactivation and/or formation of degradation products that can be harmful, especially when the active principle is particularly sensitive to thermal variations or is photodegradable. Also pollution with pathogens and adulteration with foreign substances.(29)	Toxic levels of chromium in capsules produced by 13% of China's manufacturing sites that manufacture this particular pharmaceutical form.
Untreated disease progresses and the condition of patients worsens, ending, in some cases, at death. These products may, contain inert and harmless substances or an active ingredient that does not treat the disease but may mask the symptomatology.(29)	Paracetamol in falsified antimalarial medicines, reduce fever, but are totally ineffective against the Plasmodium that causes malaria. Untreated disease progresses and the condition of patients worsens, ending sometimes at death.
In Ghana, maternal mortality rate is estimated at 350 deaths per 100,000 live births and most deaths are due to postpartum hemorrhage. (29)	Recent research has shown that 89% of anti-hemorrhagic, marketed in the territory, have a dose of the active ingredient below international standards.
Lack of correspondence between the substances declared on the label and the actual ones.(29)	Even the presence of a single undeclared excipient can be extremely dangerous for allergic or intolerant people.
Supply-side demand (29)	Incorrect use of steroid -containing creams to decolorize the skin and steroids for bodybuilding have generated a large international market.
Doctors buy fake drugs from unapproved suppliers, at prices below the current ones. (30)	Counterfeit cancer drugs such as bevacizumab (Avastin) .
The infringement of patent rights when there is the unauthorized production, use, sale, importation of a patented active ingredient or excipient, or use of a process or method. (31)	For instance, " Levitra " in China.
The launch of a counterfeit prior to the actual marketing authorization for the genuine product.(31)	This happened with Rimonabant , a drug to treat obesity. It was advertised for sale over the Internet in March 2006, having placed the genuine product on the market, prior to its authorization by the European Commission.
"Lifestyle Medications" improve male sexual performance or increase the sense of well-being. Lower doses lead the patient to take several or repeated doses, facing unavoidable damage.(29)	There are counterfeits of PDE5 inhibitors , Viagra, Cialis, have active ingredient to treat erectile dysfunction capable of causing erection increases with the risk of having an adverse effect.

(*) Another counterfeiting practice is **to prolong the original and approved shelf life by replacing the date label, or repackaging the drugs with altered-date labelling**. In this case, the pharmaceuticals have been obtained at low cost due to their being very close to, or having passed their approved expiration date.(31)

5.8. ANALYSIS OF THE DILEMMA

The '*Cracking Counterfeit Europe*' study, conducted by Pfizer in November 2009, seeks to assess the real size of the illegal drug market in Europe through an online survey on counterfeit medicines. **14,000 people in 14 European countries** are taken into account to analyze consumer attitudes aimed at educating people about the risks of acquiring prescription drugs through illegal channels and to make consumers aware of their treatments under medical prescription and always within the legitimate health systems.(21)

The results of the study suggest that:

The counterfeit medicines market could exceed **1.5 billion euros annually**, and **14.3%** of the total European black market total is **10.5 billion euros**. **Almost one in three Spanish people (29.8%)** surveyed admit to having acquired prescription drugs through inadequate or illicit practices, which means that some **11 million** people in our country practice this inappropriate consumption. **The European average** of people who buy prescription drugs through inappropriate or illicit practices is **21%**, which puts **Spain in fourth position**, behind Germany 38%, Italy 37% and Norway 30%. (21)

The survey continued with this simply question:

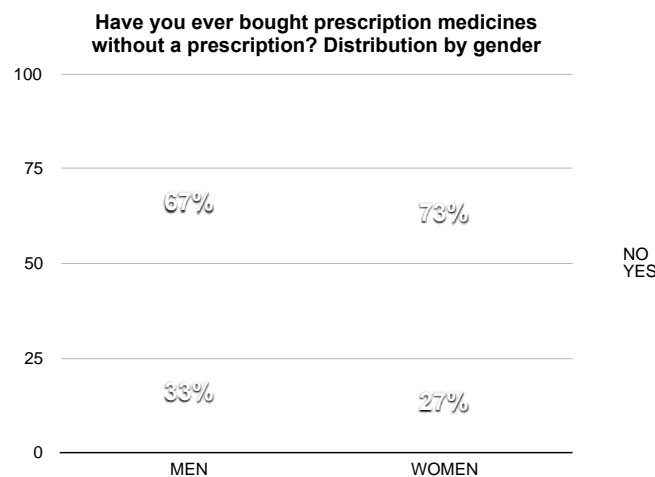


Figure 17: Spain illegal acquisition of medicines. Adapted from(21)

The results of the study also show that in Spain, the acquisition of drugs that must be prescribed by a healthcare professional without prescription is slightly higher among the male population (33%) than the female (27%).(21)

The most consumed online medicines without prescription when needed are:

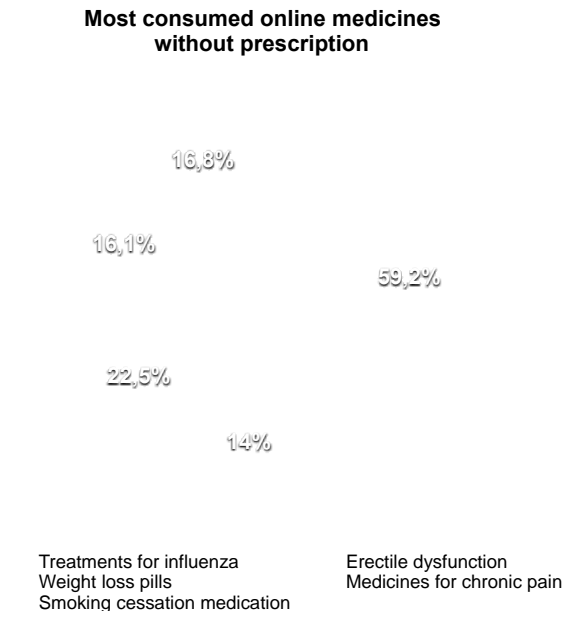


Figure 18: Most consumed online medicines. Adapted from(21)

(*) It should be noted that the survey was conducted in November 2009, in the midst of the media boom of influenza A.

Among people in Spain who admitted buying prescription drugs through inappropriate or illicit practices, **almost one in five (18%) did so through the internet**. Of these, **more than a third** of purchases were made through foreign pages, and **20% were made after receiving advertising** on these medicines through spam mail. And according to the study, **24% of the respondents**, who admitted to having acquired drugs through non-established channels, detected that **the medicine was false, 40%** considered that **the medicine did not work and 37%** said that **it was not safe**.(21)

The following graph reveals that the main reason people get prescription drugs on the Internet is the saving of time and money, the economic issue being more important than the issue of time.

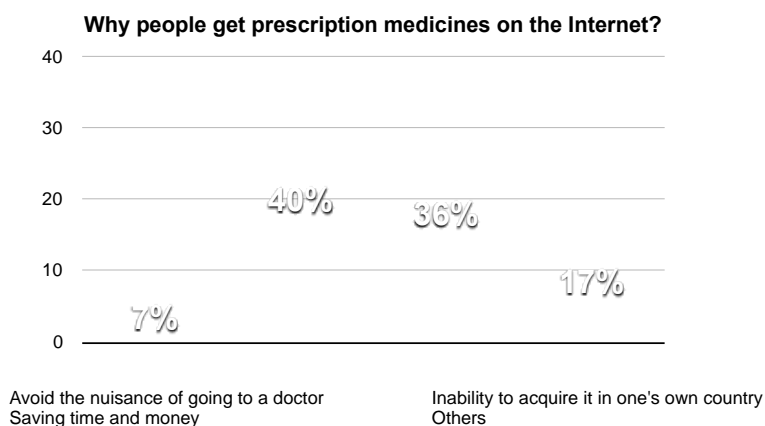


Figure 19: The main reason people get prescription medicines on the Internet. Adapted from (21)

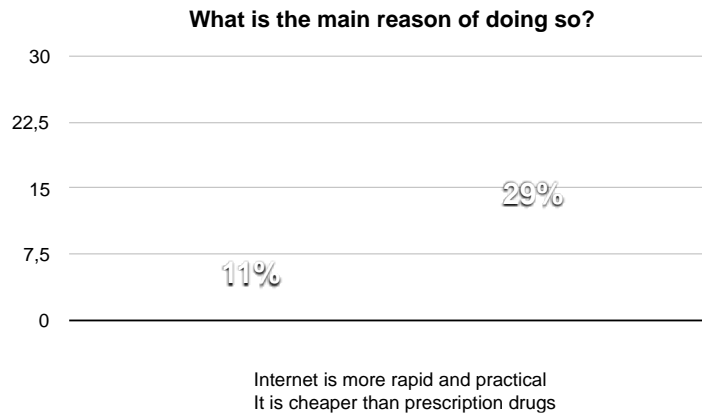


Figure 20: Internet is more practical or cheaper? Adapted from (21)

In addition, **one of every ten Spaniards interviewed doesn't care about the authenticity of products purchased through the internet while 21% consider that a prescription medicine purchased over-the-counter is always authentic.** There are evidences about the ignorance of patients about medications require medical prescription and which do not, for example: 30% unknown Reductil need recipe, 26% in the case of Viagra®, a 21% compared to Cialis, 19% in relation to Xenical and 11% regarding Tamiflu.(21)

According to the results of the study, one of every five Spanish respondents, or extrapolated to the percentage of the total Spanish population, more than 7.5 million people in our country, does not consider that consumption of drugs for which makes no prescription without a prescription is a risk to your health. This situation contrasts with the fact that 59% of respondents worry about risks to their health and 24% by the effectiveness of the medication.(21)

Would you buy medicines on Internet if you knew they are fake?

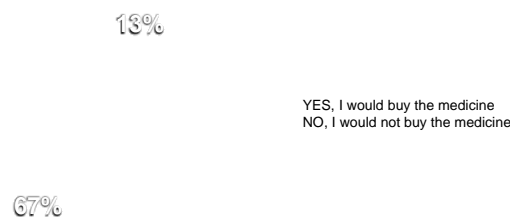


Figure 21: Percentage of Spanish people who would or not buy on Internet knowing the medicines are fake. (21)

More than two-thirds of the Spanish population 67% would not buy medicines over the internet if they knew to be false. However, still a worrying 13% of respondents in our country said that the possibility of a false medicine would not impact on its intention to purchase it.(21)

5.8.1. PUBLIC AND PERSONAL HEALTH CONSEQUENCES

More than 4 billion people, roughly half the world's population, live in countries where medicines are not effective because of their counterfeit. This pandemic of adulterated medicines condemns without the appropriate treatment to patients that suffer serious illnesses.

In all cases the origin of a counterfeit medicine is unknown and its content unreliable. Many of the counterfeits are, antibiotics, contraceptives, anti-tetanus, antimalarial, erectile dysfunction, drugs used for organ transplantation, cardiology drugs, anti-schizophrenia drugs, anticancer drugs, etc.(32)

A medicinal product can only be marketed when the health authority (AIFA, EMA) has assessed that the **risk/benefit balance is favorable**, based on the results of the studies to which the drug has been subjected. These conditions are specified in the marketing authorization of the medicinal product and are included in the technical data sheet and in the package leaflet. This positive opinion guarantees the efficacy and safety of a medicinal product and is strictly limited to the conditions established by the experimental procedures as treatment of a well-defined disease, at precise doses and intervals, exclusion of pathologies, contraindications, risk of adverse reactions, etc. Any other use other than the medication is not indicated, there is no guarantee of efficacy. (33)

At patient level

According to WHO and reports from international organizations, counterfeit medicines can give four situations:(22)

- **No active principle ingredient:** As a consequence, patients do not receive any treatment and can worsen their state of health.
- An **insufficient** amount of API: As a consequence, the drug may not be effective in treating the patient. It can be a therapeutic failure or resistance to treatment. Prescribers may consider increasing the dosage what can evolve to an increase in side effects, injury or death due to unintentional overdosing by counterfeit medicines. Another alternative of action for the doctor is the change to a second-line treatment, which may be more expensive or have more side effects than the previous one.
- An **excessive** amount of API: In this case, the patient will be more likely to suffer adverse reactions.
- **Toxic ingredients:** Unusual symptoms may appear and could misunderstand the diagnosis and avoid the correct treatment. Depending on the disease could lead the patient to death. The pharmacological effects of absorption, distribution, metabolism and excretion of drugs are especially critical for drugs with a narrow therapeutic index, for example: warfarin.

At society level

All countries are affected by this illegal and criminal activity, but especially the developing countries, being the main target for the counterfeiters. This is because the cost of legitimate medicines goes beyond the reach of a large number of citizens, where the National Health Systems (SNS) are deficient, facing restrictions on adequate supplies, lacking sufficient human, technical, Materials and laboratories for verification. Poor people are desperately seeking options that are more affordable to their precarious economy, making them easy victims not only of counterfeit but also sub-standard medicines.(33)

These spurious, misleading, falsified or imitation medicines deliberately and fraudulently attack Human Rights and the Right to Health. It is clear that they erode public trust in health systems, in health professionals and workers, affect the credibility of industries, and even worse, their presence undermines the credibility and reputation of national authorities and enforcers the law. A single case of drug counterfeiting is already unacceptable and indicates that the pharmaceutical delivery system in which it was detected is vulnerable.(33)

5.8.2. EFFECTS

The counterfeiting effects are very varied and can be analyzed, since in many cases are not taken into consideration, some aspects which can cause a major social, health and economic troubles such as:(34)

Expense on trust of the patient, both to the drug that has consumed and to the professionalism of the health care professional who dispenses or manages it.
Deterioration affecting public health. This disorder can be harmful in several ways. The first one is in relation to toxicity, since they frequently cause physical damage, partial or fatal, also if the quantities of active ingredient are not appropriate, possibly medication does not have efficacy and its consequences are similar to the previous case.
Thirdly, it should be taken into consideration that the emergence of new strains of viruses, parasites and bacteria resistant to drugs, promotes less than the correct dose as the active principle of the drug does not eliminate all pathogens allowing the proliferation of resistant strains. These problems have been observed in many diseases, of which we highlight standard of health as of scientific publications that have more importance. They are the case of malaria, VIH and bird flu.
They can affect the health care system, since the use of these substances causes adverse effects and variation to pathological level which may lead to new treatments and hospital stays, which in many cases are of great economic cost.
Disorder in the proprietor of the registered trade mark, since it affects your reputation and image of the laboratory that marketed the drug.

5.9. HOW TO DETECT A SPURIOUS MEDICINE

Visual inspection (22)

Sometimes spurious products appear to be extremely similar to originals so their identification may require chemical analysis. However, visual inspection is sufficient in some cases. We must look for inadequate packaging, labeling, dose description, errors, lack of information on concentration, dosage or expiration date. A comparison with the authentic pharmaceutical product is always preferred.

Check the packaging (35)

1. Make sure you know what every aspect of your medicine's packaging looks like, including the blister pack or dispensing system.
2. Every time you renew your prescription, compare these aspects with your previous pack. You are looking for even the tiniest difference in clarity of print, color, seals, etc.
3. Check that the medicine is in date and that the dosage is correct.
4. Check that there is a patient information leaflet in the correct language.

Selection of suppliers (22)

In many cases, the infiltration of spurious medicines within the legitimate pharmaceutical distribution chain is made possible through an operator of this chain buying from an unauthorized seller/unofficial seller.

Check the medicine (35)

If, when administering a drug, whether by the division of a tablet or the dispersion in a glass of water, differences in the characteristics of the product are observed, it is necessary to suspect. When treatment fails, healthcare professionals should consider spurious medicines as a potential reason for non-response or for an unexpected response in pharmacotherapy.

Check carefully that it is consistent in color and texture with your previous prescription.

1. Does it crumble?
2. Is the color different from your normal medicine?
3. Does it smell or taste different?

If you notice any differences in appearance, report them to your pharmacist and your national regulator straight away.

5.9.1. TOP TIPS (35)

Talking to your doctor

Make sure you go to the doctor before using any medication for the first time as he will review your history and prescribe the right medication to treat your condition.

There are times when you may be ashamed to talk to your doctor if the issue is embarrassing but you have to make the effort to have the best diagnosis and treatment.

Patient groups

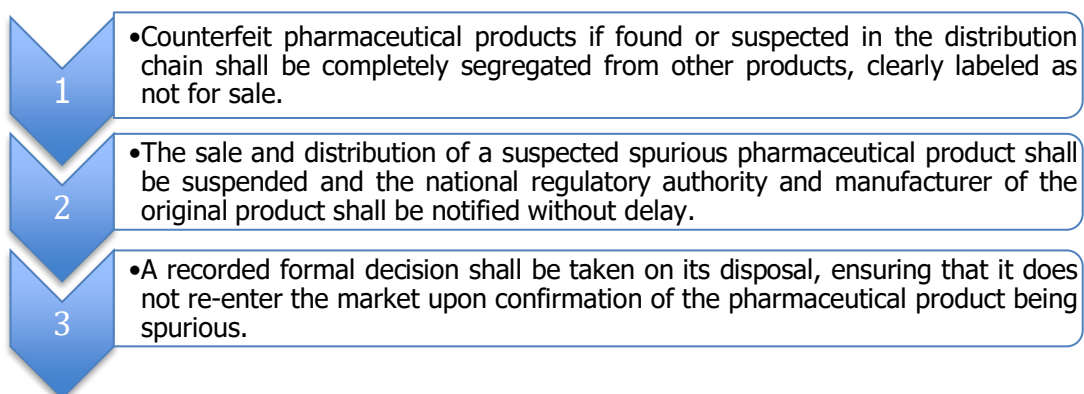
Patient groups offer support to people who seek advice and provide educational material. However, going to groups of patients is not substitutable with going to the doctor. However, they can be helpful in guiding and solving any problem.

Your medication

You should tell your doctor if your medicine is not working as usual or if you notice any side effects. Reviewing medications regularly reduces the risk of taking a counterfeit medication.

5.9.2. HEALTHCARE PROFESSIONALS PROTOCOL IF THEY FIND A SUSPECTED SPURIOUS PRODUCT

The procedure to follow as per Good Distribution Practices (GDP) Guidelines of CDSCO, if spurious medicines are found in the supply chain:(22)



6. CONCLUSIONS

The counterfeiting of medicines is a major problem worldwide, affecting all countries in different ways. Apart from solving the counterfeit drugs problem is important to ensure that patients do not lose faith in the benefits of pharmaceuticals and become nonadherent with their treatments. The expansion of the Internet, and the difficulty in controlling drug suppliers from the Internet, have greatly increased consumer purchases of counterfeit drugs. Definitely, harmonization, at international and local level in regards to definition of counterfeit medicine and coordination, is needed to ensure appropriate regulation, control and research.

Furthermore, to measure the real extent of the dilemma and its impact, especially in countries in the process of development, Africa, Asia and Latin America, is difficult since the percentage is higher. As we have seen in the factors section, increase of intermediaries and non-existent regulation, increases trade in fakes. Another cause of the proliferation of this market is the price differences of some countries to others, since it is not regulated or do not possess adequate reimbursement schemes, and may cause the patient to look for cheaper alternatives.

Consequences observed in human health show that the risk is not so hypothetical. The possibility of consumption of spurious drugs is proportional to the number of selling illegal drugs. It is extremely difficult to detect the cause of the disease if there is doubt of having eaten a counterfeit medicine. For this reason, doctors play a crucial role to curb and prevent the phenomenon, especially in older people because many are polymedicated and can have more interactions between them. It should be added that consumption of counterfeit medicines represents an increase in the burden to health due to increased hospital admissions. Undoubtedly, it is necessary to provide more information to patients and professionals health risk involving the consumption of this type of medication.

Another conclusion is that serialization can provide significant benefits beyond compliance. The main advantage of the serialization strategy is to provide an enhanced security to medicines so that they reach patients in an integral way, safeguarding that laboratories continue supplying and complying with the regulatory requirements. The new guidelines on good distribution practice are far more detailed, reinforcing the requirements of the management system of quality checks on suppliers and customers, important for the safety and transparency of the chain and distribution entities. The patient's safety is, without any doubt, the main benefit, but also to protect the brand. The advertising associated with any counterfeit incident creates a significant threat even for the strongest brands.

Another benefit associated with the serialization is the significant impact that can have on the reduction of products withdrawn from the market from the perspective of labelling. In general, technology and controls validation processes will improve, therefore, errors will be reduced significantly. It should also improve the speed of withdrawal of those products already placed on the market. Other positive impacts will be the automated greater visibility of the products. Therefore, we will observe an improvement for the control of expiry date and stockage although not its primary function. Moreover, the seal coupon will disappear in a future, as happened in the case of France, to improve the refund.

The fight against counterfeit medicines should continue and be strengthened by Member States, organizations of the United Nations and non-governmental organizations, pharmaceutical industry, health professionals and consumers. Although in our society, we are experiencing a progression in the awareness of the harmful effects, there is still so much to be done requiring greater cooperation and collaboration between Governments and organizations.

To conclude, Farmaindustria will make a huge investment in the hope of later recover the benefits of eliminating the counterfeit. Also note that the implementation of the regulation in Spain will be a little late. If we want to achieve the goal, it will require the effort of all stakeholders of the pharmaceutical sector in a near future. The changes in this new Regulation will make Spain a more modern, efficient and competitive sector.

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