UNIVERSITAT DE BARCELONA

FACULTAT DE FARMÀCIA I CIÈNCIES DE L'ALIMENTACIÓ

FALSIFIED MEDICINES, VERIFY BEFORE YOU BUY

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ABSTRACT

Falsified 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 been analyzed the evolution of European legislation and safety devices, the detection of spurious products, regularization, control and their consequences, advice for the patient and the incidence rate, are some of the topics covered in depth in this assessment. Other aspects, such as factors that influence adulteration are also described. It is urgently needed, improvements in surveillance, including the detection of breaches of security, collection, analysis and dissemination of data to address the requirements of public health to combat the global trade of spurious medicines. In conclusion, the main purpose of the current legislation is to ensure consumer's safety 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 todos los envases de medicamentos de prescripción vendidos en el mercado español. La industria farmacéutica, mayoristas y oficinas de farmacia deberán 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 del mercado. En esta revisión, se ha analizado la evolución de la legislación Europea entorno a los medicamentos adulterados, se han 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 que son algunos de los temas tratados en profundidad en el presente trabajo. También se repasan otros aspectos como los factores que influyen en el fraude. 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 alterados. En definitiva, 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 overview includes three different fields of study, but they are all closely related. The new *Delegated Regulation (EU) 2016/161* raises a series of new aspects that pharmaceutical companies have to take into account in case they want to launch products in the market, especially the ones that have more index of falsification. Throughout the survey, 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. Unfortunately, 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 examination 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 ahead. Besides the original medicines have to follow a study, in order to find, notify and withdraw from the market, adulterated 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. Additionally, the modified 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 the safety devices that are incorporated in the outside packaging of the drugs.

2. INTRODUCTION

2.1. HISTORY

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 result was 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 falsification. 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)

Because WHO has been working on this complex and politically sensitive issue since the **World Health Assembly**, law enforcement activities were intensified in 2006 when **IMPACT** was established. IMPACT is composed of international organizations, law enforcement agencies, the pharmaceutical industry and non-governmental organizations.(2) Althought the subject did not reach an international level until 2013 at the **MEDICRIME Convention**, held in Madrid. From that convention came out the legal framework for national and international cooperation between health authorities, the police and customs officials in the fight against falsified products, including medicines. After that a total of 23 countries, including Spain, were adhering to this initiative.(3)

The entity that leads the fight against spurious 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 acquiring illegal drugs through websites. In parallel, the AEMPS is working on a proposal for the crimes related to illegitimate drugs trafficking to be included in the Criminal Code in the framework of crimes against Public Health, due to the risks associated with patients' health. (2)

In recent years, people without any concern, were exposed to the intake of dangerous substances, in some cases potentially lethal. It could be concluded that this irrational and misguided attitude could come from a mistrust in official medicines.

2.2. THE CONCEPT OF FALSIFIED 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 falsified medicine is a product deliberately and fraudulently mislabeled as to its identity or source. Falsification affects both branded and generic products. Flasified 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 a 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 all the paper, the terms spurious, falsified, counterfeit, aldulterated are considered as interchangeable.

3. AIMS

The goal 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 falsified 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 fake products are removed effectively and quickly from distribution channels. Therefore, in order to facilitate the work of the inspectors, it is required the collaboration of experienced organizations that participate in the distribution chain to easly identify non-genuine medicines. To summarize, the current legislation aim is to ensure consumer safety and also the perfect running of the supply chain delivering original drugs within the EU.

The overview is focused on policies related to interventions in public health and education/awareness, regulatory measures, and some tips to avoid the intake of manipulated medicines. However, another purpose is to describe the new anti-tampering technologies and their future implementation in 2019. Also, the economic impact that the regulation will entail and its timetable for compliance. Other targets are to analyze the market, influencing factors, consequences and effects of the corrupt medicines at a European and Spanish level to reflect the magnitude of the dilemma and ilustrate the national strategy to follow to timely detect falsifications. We will not focus on altered medicines purchased online because it is a very extensive subject. However, it has been used Pfizer results with the challenge of representing data graphics on the global situation of the matter.

Finally, the ultimate goal of the report is carrying out an interview with a specialist on the issue, such as Mónica Soler from AECOC. The direction of the interview deepens in the Data Matrix code with the unique identifier and the anti-tampering devices characteristics to clarify the different shades of the verification system roles, as well as having a broad view of the changes implementation that will take place in the outside drug packaging pursuant regulation.

4. MATERIALS AND METHODS

The essay methodology consists of an assessment of the current situation through a review of the legislation. The study is focused specifically on the emerging technology, the 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 government webs 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 examined 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, traditional forms of authentification and packaging serialization.

Finally, I had the opportunity to attend 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 system. Being of great help for the information given about the development and validation of alternative methods of verifying an original medicine.

5. RESULTS AND DISCUSSION

5.1. LEGAL FRAMEWORK

Falsified medicines pose a borderless risk to the health of patients and health authorities around the world which are developing various initiatives to address this problem. In the case of Spain, they have been implemented since 2008, by the AEMPS. A four-year strategy has been carried out since then. This strategy complements the national regulation, derived from the European legislation, against the falsification of medicines promoting the actions of all the sectors involved.(3)

The actual situation uses the following ***Directive 2011/62/EU*** amending ***Directive 2001/83/EC*** to establish a **community code related to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products**. This Directive lays down the rules for, inter alia, manufacturing, importing, placing on the market, and the wholesale distribution of medicinal products in the Union as well as rules relating to active substances. Past experience shows that such falsified medicinal products do not reach patients only through illegal means, but via the legal supply chain as well. This poses a particular threat to human health. That is the reason why the Directive, which is used as a macro level, should be amended in order to respond to this increasing threat. It also entails international audits, reviews, inspections, sanctions of all forwarding agents, drug control over the internet and the basic elements for the development of a European model placing safety features, which will allow in a near future the verification of the authenticity and identification of individual packs and provide evidence of tampering.(6) This safety features for medicinal products should be harmonised within the Union in order to take account of new risk profiles, while ensuring the functioning of the internal market for medicinal products. On the other hand, the Delegated Regulation describes in depth the features of this Directive. (Annex)

Thus, the system has been developed from the existence of the **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 what new tools will provide to prevent the entry of fake 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 features have been included such as the unique identifier and the anti-tampering device to ensure the safety of medicinal products. Other 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 controls and inspections of manufacturers of active pharmaceutical

ingredients and last but not least strengthening requirements for wholesale distributors.(8) However, this regulation does not provide of technical options for the anti-tampering device, which choice of the most appropriated device is left to the manufacturer. (Annex)

5.2. THE FALSIFIED 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 is an effective market regulation and control systems, whereby adulterations have an incidence of less than 1% of market value. On the other hand, it is indicated that in USA the world sales of imitation drugs could exceed USD 75 billion annually with a 90% increase in five years, estimations published by the Center of Medicine in the Public Interest of the United States of America.(9)

Besides, counterfeiters use varied, flexible and intelligent methods to imitate the products prevented from 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 its distribution does not help to easily stop their market circulation. They infiltrate the legitimate supply chain and also use unlicensed online pharmacies to mix fakes between the legal ones.(9)

The factors that determine this activity are mostly desire for profit, commercial voracity, high prices, worldwide growing medicines demand, the disparity meanings of falsifying, which hamper legal action, the expansion of international trade in pharmaceutical principles and medicines, as well as multiplication offers in the internet. This issue affects both brand and generic products.(9)

5.3. FACTORS FACILITATING FALSIFYING

A wide variety of factors contribute to the proliferation of spurious drugs and cover such broad causes like national drug policies, health coverage or poverty. They need to be accurately identified in order to enable governments to detect falsification troubles and introduce effective programs to eradicate fraudulent drugs in the national 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 all manufacturing establishments are adequately inspected. If not, it can lead to the promotion and a greater commercialization of the spurious drugs. Insufficient human and financial resources for drug control activities could also facilitate the inability of the national drug regulatory authority to investigate 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, factors that could cause the 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)

Absence of law enforcement

When laws are not envisaged, there is a tendency to perpetrate crimes such as falsifying, as the fear of being arrested is minimal. In addition, non-observance of trademark rights may lead to a large-scale issue.(10)

Weak penal sanctions

Absence of or lenient penal sanctions for violations of drugs legislation it is one of the factors that make a difference to the progress of this illegal activity. The goals of the Medicrime Convention are to include in criminal law offenses related to spurious medicines.(3)

Corruption and conflicts of interest

Inability to arrest, prosecute and convict those responsible for counterfeiting. Furthermore, 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 falsification is a very lucrative business due to the intense and constant demand for medicines and the low production costs. When drug desire exceeds sanity, counterfeiting may be encouraged of taking large profits made from the manufacture and distribution of manipulated products. Sometimes a higher demand is generated through the inappropriate consumers use of drugs. For example, the misuse of steroid-containing creams for bleaching the skin and of steroids for body-building have created a large international market for perverted steroid-containing drugs which 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, encourage patients to seek the best prices and cause fierce competition among sellers providing opportunities for lawbreakers offering more affordable prices. Therefore, there is a greater incentive to supply cheaper counterfeit drugs.(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 lawbreakers 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 delinquents arrested to date carried out their activity in ordinary houses, in small domestic factories or simply in the backyard 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 falsifications 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 the country consumption. 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 falsified medicines that have reached patients in Spain through the legal dispensing channel. However, outside this channel, spurious medicines, as well as products adulterated with active ingredients not declared in their composition, are detected.(3)

Lack of social awareness

Illiteracy, poverty and a lack of social awareness pose a disadvantage for patients to fight against falsifications. (10)

5.4. THE NATIONAL STRATEGY

Medicine's adulteration is a global matter that affects us all. The traffic of this products generates the activity of 25 times more profitable than selling drugs and if it increases, will for sure threaten the drug marketing and public health with really worrying numerical figures. They could be approximately 10% of the global pharmaceutical market and in some countries, represent even the 50%. What they all have in common is that most of these are purchased online.(4)

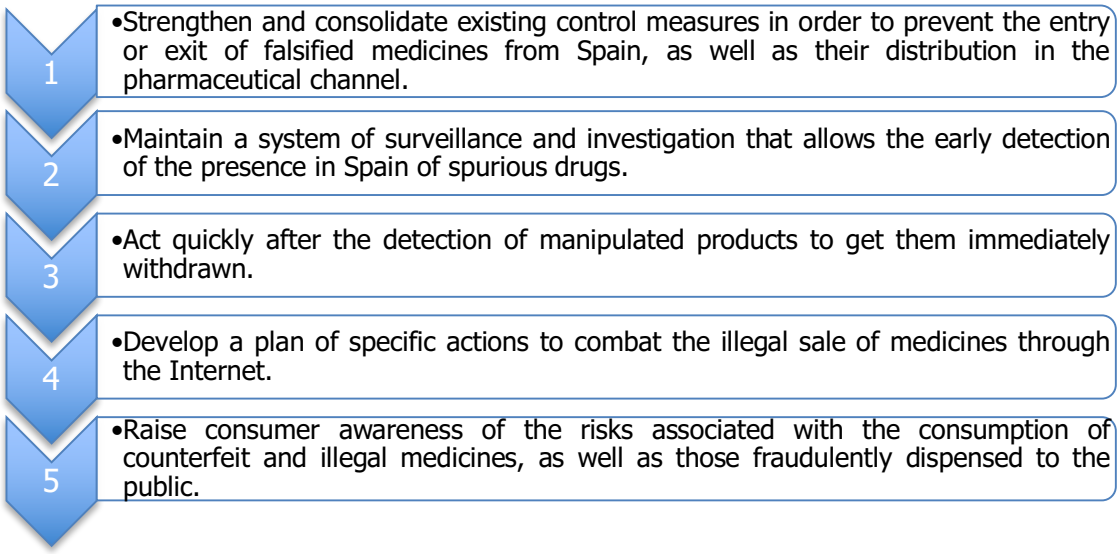
The evaluation of deaths due to falsified drugs vary from tens of thousands to more than 200,000. Unfortunately, lawbreakers are skillful in copying the packaging and appearance of real drugs. Sometimes you cannot confirm whether a product purchased online is authentic or not until a chemical analysis 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. Spurious medicines can escape all controls as a result of an accelerate 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 dangers associated with the consumption of fraudulent 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 falsified 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 fake 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 fraudulent 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 drug sales without prescription online. There is a shared responsibility by both the distributor for selling the altered medication and also by the pharmacist for performing drug testing before selling it. (3)

We are fortunate enough that in Europe and in Spain it does not reach a 1% and if it does so it has always occurred in channels outside the law. Also 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 Falsified 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 Data Matrix 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)

This 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)

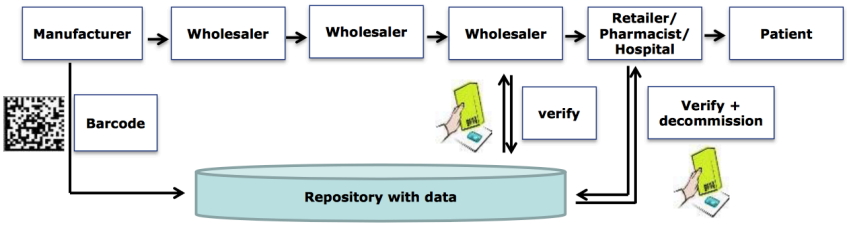


Figure 1: End-to-end verification system + risk based verifications. Adapted from (12)

What is pursued with the drug verification system is to prevent tampered drugs in the legal supply chain, with each drug packaging being distinctive 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 identificator 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. Moreover, the role played by the AEMPS is to enter, monitor, but it is not part of the society that constitutes the SEVEM nor the EMVO. (13)

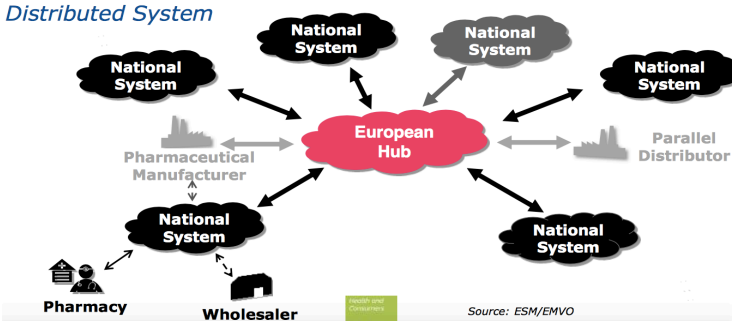


Figure 2: Repositories System Architecture. Adapted from (12)

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 seal cupon.** 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, althought they have a low price and there is not a high risk of corruption as for the brand drugs.(14)

5.5.1. SAFETY DEVICES IN THE EUROPEAN UNION

Directive 2001/62/EC lays down the safety devices types and their function. Commission authorities concerning medicines will notify the criteria to define which drugs will requiere them or not and the extent of its use and information system. (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).

Authorized medicines in Spain that must be carrying safety devices are all prescription drugs, except those listed in **annex 1, so-called white list.** As well as non-prescription medicines that must carry them, listed in **annex 2, so-called black list**. It is a remarkable fact that each country will have its own list(7) and also that each Member States will extend the scope of the application deciding what drugs will wear the UI or the ATD according to the *Directive 2001/83/EC.*

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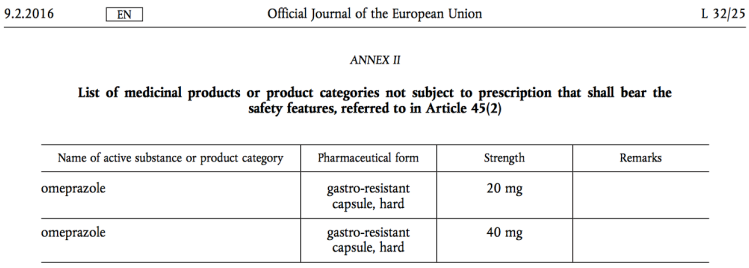
ANNEX I

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)



9.2.2016 EN Official Journal of the European Union L 32/25

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)** that 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.

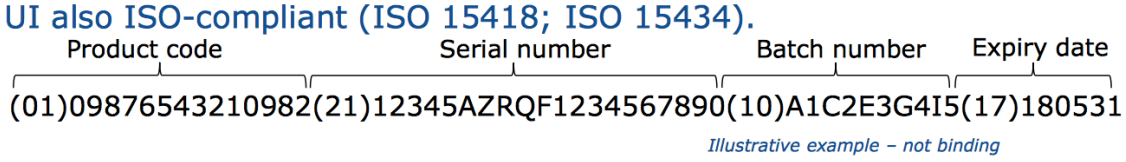


Figure 5: UI model (12)

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 up to an 80% it could be still readed. This residual storage capacity will be used to include more information without putting other barcodes. Also, 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 and the act of dispensing. It must be avoided the chance that the packaging of a drug takes several two-dimensional bar codes for the purpose of verification and identification.(7)

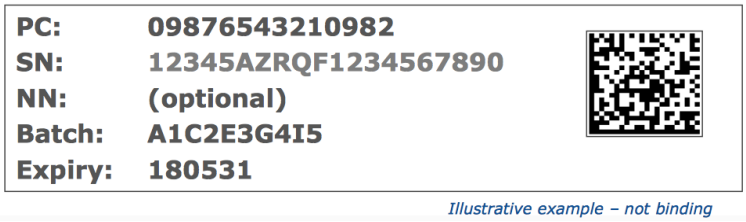


Figure 6: Data Matrix model (12)

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. It should be clarified that 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) Moreover, manufacturers must keep records of transactions on the unique identifier of a drug after its deactivation in the repositories system 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 the Data Matrix. The objective is to **eliminate the print of the national reimbursement number** and insert it in the Data Matrix code to prevent from duplicating 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) For this reason, there are two possibilities: (Annex)

1. Include directly the national code of each presentation in the Data Matrix, which means **increasing its size** because it must have 5 lines for the industry: expiry date, batch number, serial number randomized, national code and 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 authentification mechanisms, due to different national or regional requirements traceability, can limit the circulation of medicines in the EU and inflates costs for everyone involved along the supply chain. Therefore, it requires applicable regulations and the creation and management of the repository system that contain information about the security devices. However anti-tampering devices, such as holograms and glued, can be applicable on all the containers that the 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 the 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 pharmacist responsible to get the information updated and control that no expired, recovered, withdrawn or reported medication reaches the public as stolen. However, some packages cannot finally be dispensed. Such is the case, for instance of drugs that must be distributed outside the EU; the ones to be destroyed or medicines that 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 system before the check, to verify the authenticity of the UI compared to the genuine one. 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 distributed. Finally, if everything is correct, the pharmacist will disable it using a common scanner.(16)

If it is unconfirmed the authenticity of the UI, the system activates an alarm and also the terminal, as a possible incident of forgery, except when the medication longer appears as recovered or removed aimed at its destruction on the screen. 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)

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 that the decommission of the UI of drugs is removed form national repositories; also to ensure the decommission of the UI of stolen drugs and indicate the reason for the following deactivation in the repositories system (withdrawn, theft…).(16) Obviously, the pharmacist will require training like all the people involved in the process. And as a last requirement, the pharmacy must have telephone support to users and a system support 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 it 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 will follow. Ctiting 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 be connected to the repository. Of course, 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, the reactivation the UI and act diligently in case of tampering or alleged falsification.(16) However, to include the safety devices (UI and ATD) we must access to the European platform (OBP), the resolutions technology supplier which protects the confidentiality of data, and loading codes; To maintain relations with SEVEM with the Operations Committee and be sure to make the payment of the system which is the implementation and maintenance phase, where manufacturers must still establish their rules.(13)

Second, **the pharmaceutical industry, wholesalers** will have to face costs to adapt the technology to the new 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).(16) Some of the distributor's responsibilities are to take measures in case of manipulation or alleged falsification; the decommission of the UI from the system of repositories and if necessary, the reactivation of the same. They should also incorporate **code readers**. In addition, 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 cases, Member States can be exempt of having the verification/decommissioning obligations if they are authorized for some certain items for public supply such as veterinarians, dentists, opticians

or paramedics. In this situation, 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) The risk of spurious medicines must be verified by wholesalers throughout the whole supply chain to minimize the risk of the ones circulating go unnoticed.

Finally, the **community pharmacies** will perform the verification of the UI and ATD before dispensing the medications; Decommission the UI and, if necessary, the reactivation of the UI, as well as to 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. Furthermore, a major investment in computers and equipment should be made to adapt the system and also buy the 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 **pharmaceutical 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

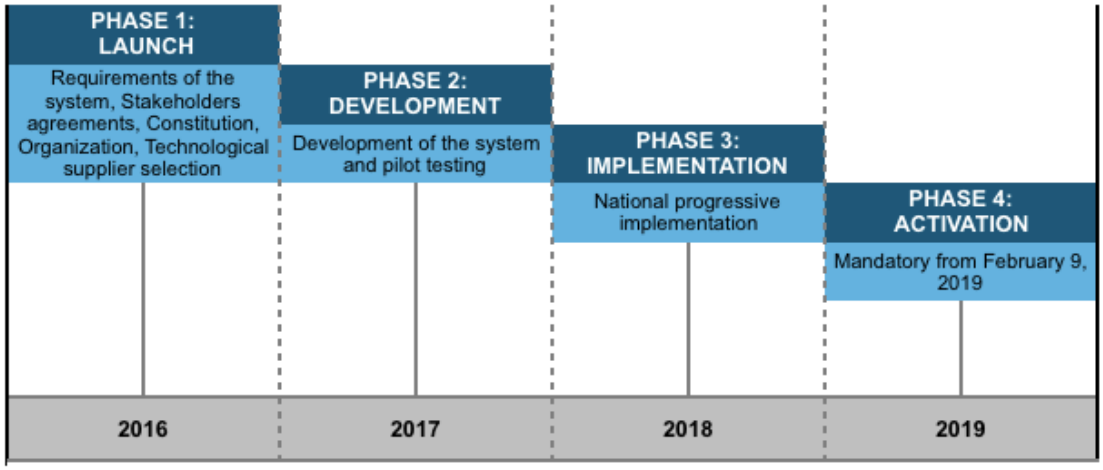


Figure 8: Implementation Schedule of the Verification System. Adapted from(11)

The implementation of the new security system has been planned for SEVEM in four phases, the first one is the **launch**. At the end of the month of June 2016, the company is formed by the different agents and, before year's end, the contracts are awarded to the technology provider. In 2017, the **development phase**, we are beging to pilot testing. In 2018 third phase, leads to the **gradual implementation** of the project in all pharmacies and hospital pharmacy services. The fourth phase, **the activation**, will begin in February, 2019, with the coexistence of prescription drugs with and without safety devices **until the year 2024**, when all prescription drugs will be incorporated into the new model.(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 dispensers in Europe. In Spain, we are actually carrying out the repository development phase. SEVEM is working on the system and its implementation requirements. It is expected to start the pilote phase with the distribution companies and pharmacies in the month of July 2017.(13)

The actual program progress is: 16 NMVOs (50%) founded, 4 contracts signed, the vast majority of countries progress and aim for Provider Contract in 2017. 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 been integrated in the 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 real change.

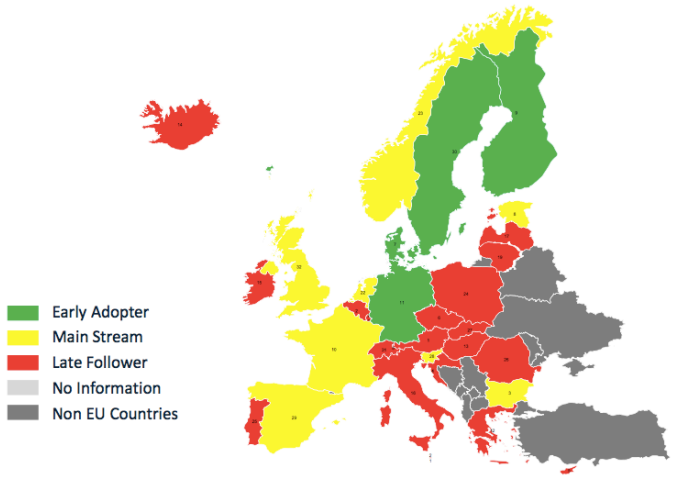


Figure 9: Executive Summary Country Readiness. Adapted from (19)

5.6.2. COST OF IMPLEMENTATION AND MODEL OF FINANCING IN SPAIN

This section could be started talking about the cost of adapting the **production lines** to facilitate unit verification of medicines that will reach 200 million euros for the industry companies 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**. Without being sufficient with that amount, 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-tampering device. It's definitely not a cheap question.(20)

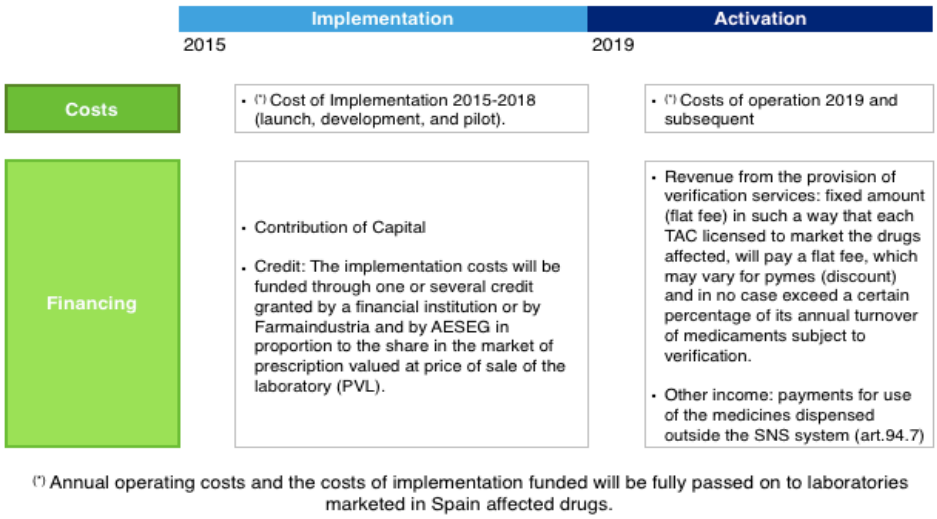


Figure 10: Basic elements of the Spanish funding model. Adapted from(11)

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 calculates 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**. It will be needed to assess whether the European Commission figures on impact are lower than the industry approximation.(20)

Another cost, although is still not tangible, is the one that will have to assume the pharmacies, the hospitals and the distribution sector to be able to read the Datamatrix codes that will appear on the packaging. 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, pharmacies will have a certain settling time and will be able to sell all the medicines that have the older model with the seal coupon for the 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 falsified medicines through non-official channels, like 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 proliferated, 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)

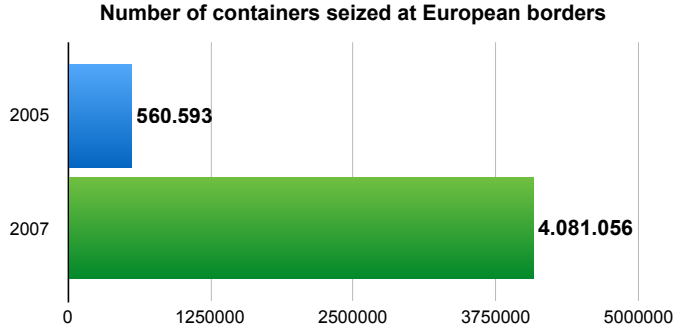


Figure 11: Number of containers seized in Europe

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 controls (e.g. USA, EU, Australia, Canada, Japan, New Zealand) currently have a very low proportion, less than 1% of the market value. However, we must keep in mind that indications point to an arise in the prevalence of spurious medicines even in such countries. Moreover, many developing countries of Africa, Asia and parts of Latin America have areas where more than 30% of the medicines on sale can be adulterated. However, other countries have less than 10%; overall, a reasonable estimate should be between 10% and 30%. On the other hand, Soviet Republic have a proportion of ilegitimate medicines which is above 20% of market value which perfectly joins the developing country range. (22)

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

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

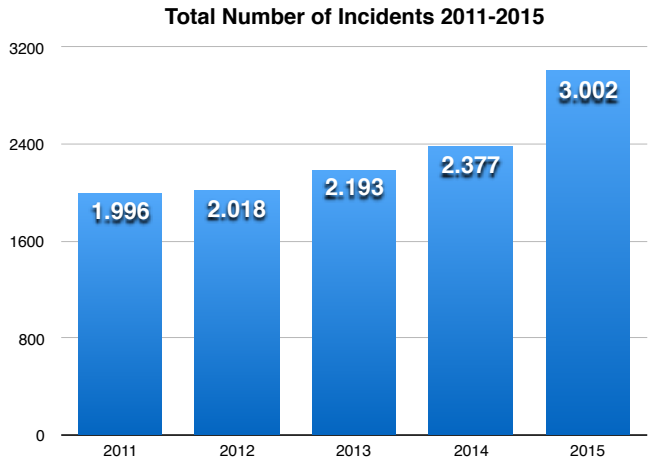


Figure 12: Total number of incidents 2011-2015. Adapted from (23)

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

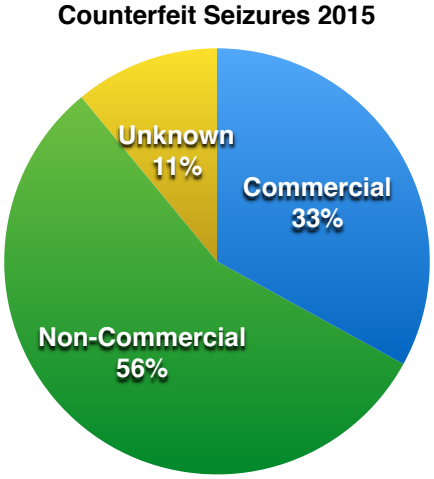


Figure 13: Counterfeit Seizures 2015. (23)

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

The conclusion that can be drawn is that both commercial and non-commercial seizures expand significantly during 2015. So it is corroborated that small-scale falsification is the most detected by the authorities and possibly the most performed by criminals worldwide.(23) Apart from the data above, in agreement with the reports of international organizations, it is also known that the theft of pharmaceutical products increased by 66%, while cases of adulteration during this period also did by a 122%. However, the true scope of the problem remains unknown.(24)

5.7.1. GEOGRAPHIC DISTRIBUTION

No continents remain untouched by this issue, from North America and Europe to Africa, South East Asia, and Latin America. With the exponential expansion of Internet connectivity those engaged in the manufacture, distribution and supply of ilegitimate products, have gained access to a global market place. A culture of self-diagnosis and self-prescribing has lead to the appearance 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 a weak or non-existent health systems, bear the greatest burden of spurious pharmaceutical products.(4)

As a curiosity, it is shown the geographic distribution of fraudulence, where data is divided into seven regions worldwide, ordered in the contiguous table below from the ones that had the highest number of events to the less. A total of 3,002 episodes were collected. With all the data, we can conclude that 128 countries are affected by drug crime. Compared with 2014, PSI recorded a thirty-eight percent growth (38%) in global affairs. In the year 2015, the impact in the Asian region surpassed for the first time one thousand scenes. In North America also rose one hundred percent compared to year 2014.(25)

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

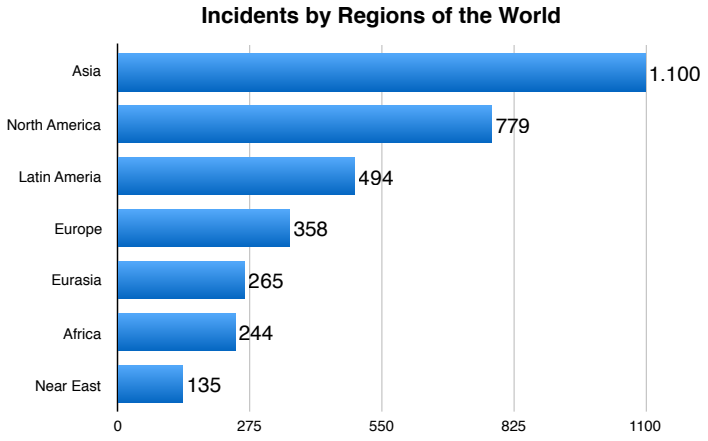


Figure 14: Data collected from incidents of pharmaceutical crime in 2015 by PSI (25)

On the other hand, other unquantified variables impact economically, for instance, the cost to public health due to the side effects for the intake of fake medicines.

5.7.2. ECONOMIC IMPACT

The imitation of medicines is very lucrative, around 75,000 million dollars. One possible explanation could be the influence of the different law involvement in each region as well as the arrests. Falsifiers do not spend money on good manufacturing practices, but invest in packaging equipment. It is unbelievable that profits become 500 times higher than the previous charge.(19)

The arrests of 1,375 people involved in manipulation, 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. Consequently, it can be concluded that the increase in crime may be due to the decrease in arrests.(26)

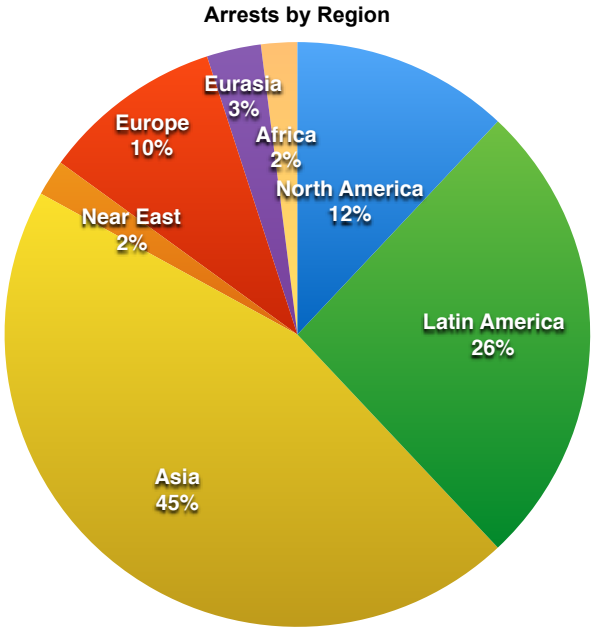


Figure 15: Arrests by Region (26)

An actual case of counterfeiting is what happened to Pfizer in 2010. As claimed by the company data, authorities in 53 countries confiscated 8.4 million tablets, capsules and vials of Pfizer imitated products, ranging from Norvasc (for hypertension) to Zithromax (antibiotic) and Celebrex (arthritis). Bogus pills could sometimes contain chalk, brick dust, paint, and even pesticides. The most unpleasant new was that a batch of pills originated in China, contained the remains of human fetuses. It is really a pity that companies' resources could be used for research rather than being used to fight against adulteration as it happens nowadays. (27)

To make matters worse, $75 billions of falsified drug sales is the loss of profit estimated. To illustrate the point, assuming that only 50% of the drug sales would occur at customary prices, and because spurious are most prevalent with the more profitable drugs, **the annual commercial profit lost could be approximately of $18 billion.** (28)

5.7.3. MOST AFFECTED PRODUCTS

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

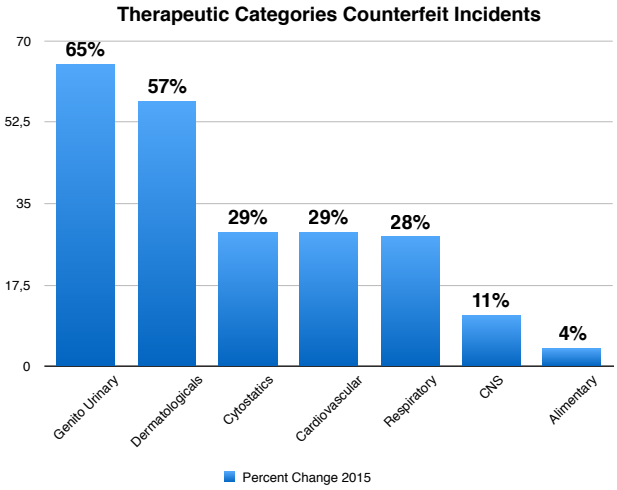


Figure 16: Therapeutic categories. Adapted from (26)

According to the analysis of falsifications, the therapeutic categories of genito-urinary, anti-infectious and central nervous system (CNS), represent the highest number of incidents. 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 growth percentage of 65%. Categories with a lower expansion were: dermatological 57%; cytostatic 29%; cardiovascular 29%; respiratory 28%; CNS 11% and nutritional 4%.(26)

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

In line with a study focused on 8 drug types by the WHO-approved list, 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 15% of **the samples failed at least one test, considering themselves poor quality drugs**. Also note that the drugs which failed the tests were priced 13-18% lower than non-failing products. **So, it was concluded that consumers suspect inferior quality when they pay less**. Besides, the study showed that the disparate price between failed and non-failing drugs was about 0.59-0.80$, which could be considerable for developing countries where a large proportion of the population lives on less than 1$ a day. Severe poverty, plus ignorance about the harm of poor quality medicines, support the decision to purchase substandard drugs. Coming to the conclusion that poverty is a reason to fall into the error of selecting lower priced drugs.(22)

This table exemplifies some real cases of drug falsification.

CATHEGORIES (*)	REAL CASES OF DRUG FALSIFICATION
The first case of the intake of a fake drug occurred in 1937. An American pharmaceutical company wanted to **increase it's sales volume.**(29)	They used **diethyleneglycol** (a toxic solvent) to make a sulfanilamide syrup, and more than 100 people died, 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)	Up to 13% of toxic levels of **chromium** in capsules produced by China's manufacturing sites.
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.
In Ghana, maternal mortality rate is estimated at 350 deaths per 100,000 live births and most deaths are due to **postpartum hemorrhages**.(29)	Recent research has shown that 89% of anti-hemorrhagic, marketed in the territory, have a **lower dose of the principle active ingredient** according to 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 a lower price compared to the current one.**(30)	Falsified cancer drugs such as **bevacizumab (Avastin**).
The **infringement of patent rights** when there is the unauthorized production, use, sale, importation of an active ingredient, excipient, 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 that treats 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 doses, facing unavoidable damage.(29)	There are fakes of **PDE5 inhibitors**, Viagra or Cialis, that have active ingredient to treat erectile dysfunction capable of causing erection increases with the risk of having an adverse effect.

(*) Another fraudulent practice is **to prolong the original and approved shelf life by replacing the expiry date, or repackaging the drugs with altered-date labelling**. In this case, the pharmaceuticals have been obtained at low cost due to be very close to, or having passed their approved expiry 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 fake 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 illicit 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 Spanish market of illegitimate medicines could exceed **1.5 billion euros annually, 14.3%** of the total European black market **which is estimated at 10.5 billion euros.**
Almost one in three Spanish people (29.8%) surveyed admits to having acquired prescription drugs through inadequate practices, which means that aproximately **11 million** people in our country practice this inappropriate consumption**.**
The European average of people who buy prescription drugs through illicit chanels **is 21%, which places Spain in fourth position**, behind Germany 38%, Italy 37% and Norway 30%. (21)

The survey continued with this simply question:

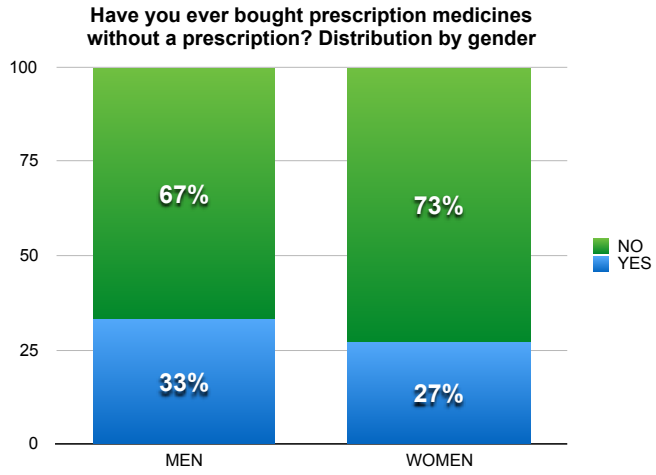


Figure 17: Spain illegal acquisition of medicines. Adapted from(21)

The results of the study also show that in Spain, the purchase 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:

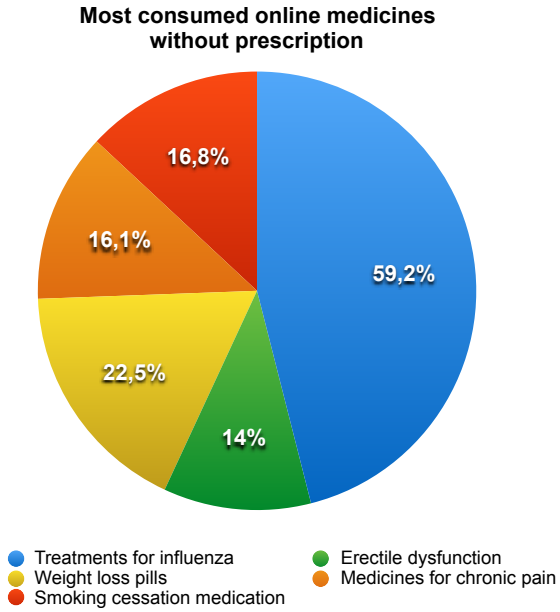


Figure 18: Most consumed online medicines. Adapted from(21)

(*) 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 illicit chanels, **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. According to the study, **24% of the respondents,** who admitted to have acquired fraudulent drugs**,** 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 the main reason people get prescription drugs on the Internet is due to saving time and money, the economic issue being more important than the time one.

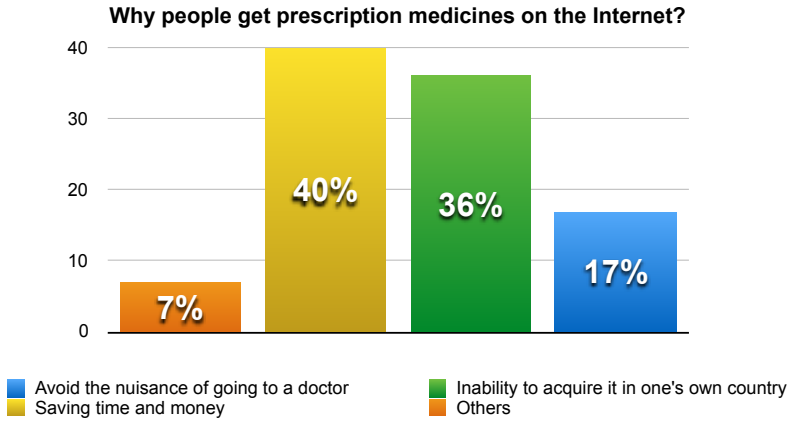


Figure 19: The main reason people get prescription medicines on the Internet. Adapted from (21)

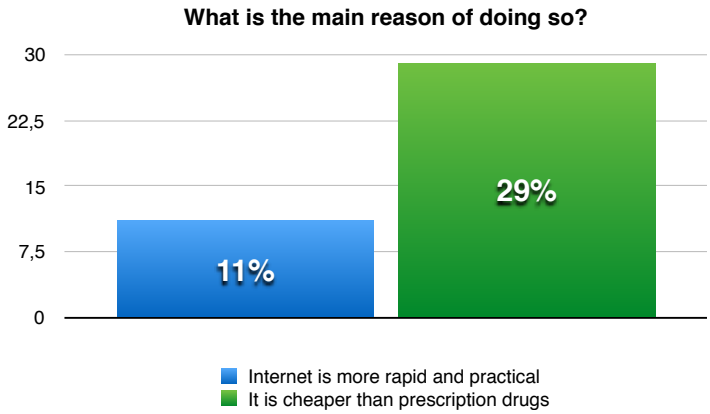


Figure 20: Internet is more practical or cheaper? Adapted from (21)

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 is evidence of the patient's ignorance related to medication. Which do require medical prescription and which do not, for example: 30% unknown Reductil need recipe, 26% in the case of Viagra, 21% for purchaising Cialis, 19% for Xenical and 11% regarding Tamiflu.(21)

According to the results of the study, one of every five Spanish respondents, 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 without prescription is a risk to their health. This situation contrasts with the fact that 59% of respondents do worry about risks to their health and 24% by the effectiveness of the medication.(21)

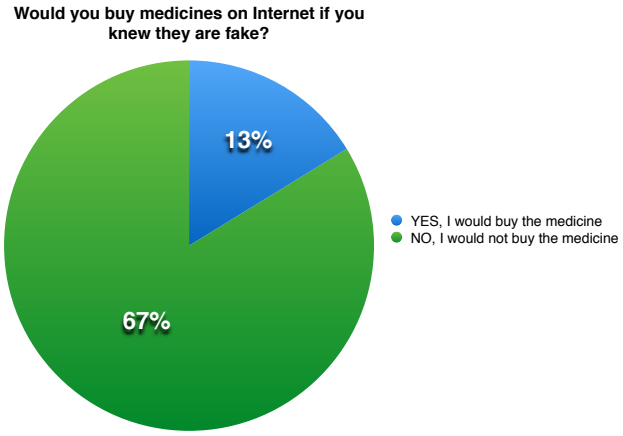


Figure 21: Percentage of Spanish people who would or not buy on Internet knowing the medicines are fake. (21)

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 they have been manipulated. This pandemic of adulterated medicines condemns patients to suffer serious illnesses. In all cases the origin of a falsified medicine is unknown and its content unreliable. Many of the imitations are antibiotics, contraceptives, anti-tetanus, antimalarials, for 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 the 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 that is not indicated, its effectiveness is not guaranteed. (33)

At a 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 could worsen their state of health.
- An **insufficient** amount of API: The drug may not be effective enough. The doctor may think that is in front of a therapeutic resistance or failure. Therefore, prescribers may opt for increasing the dosage and that could lead to more side effects, injury or patient's death due to unintentional overdosing. Another alternative could be changing the medication to a second-line treatment, which may be more expensive or again 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 a 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 citizens cannot afford the original medicines, where the National Health System (SNS) is deficient, facing restrictions of supplies, lacking of technical, materials and laboratories for verification. It might be understandable that people desperately seek for options that are more affordable to their precarious economy, becoming easy victims for falsification. (33)

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

5.8.2. EFECTS

The alteration 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 related to toxicity, since they frequently cause physical damage, partial or fatal. Due to the quantities of active ingredient are not the right ones, it is possible that medication is not effective and has the same consequences as in 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 drug does not eliminate all pathogens, allowing the proliferation of resistant strains. These problems have been observed in many diseases. It is 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 a pathological level that 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 the 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 the expiry date. It should not be forgot that 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 has not expired 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 possible through an operator buying from an unauthorized seller/unofficial seller.

Check the medicine (35)

If, when administering a drug, differences in the characteristics of the product are observed, it is necessary to suspect. Even if it is by the break of a tablet or because it has a different dispersion in water. When treatment fails, healthcare professionals should consider spurious medicines as a potential reason for non-response or for an unexpected response in pharmacotherapy but it not always the case.

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

1. Does it crumble?
2. Is the colour 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 to your national regulator straight away.

5.9.1. TOP TIPS (35)

Talking to your doctor

Make sure you go to the surgery before using any medication for the first time as they will review your clinical 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

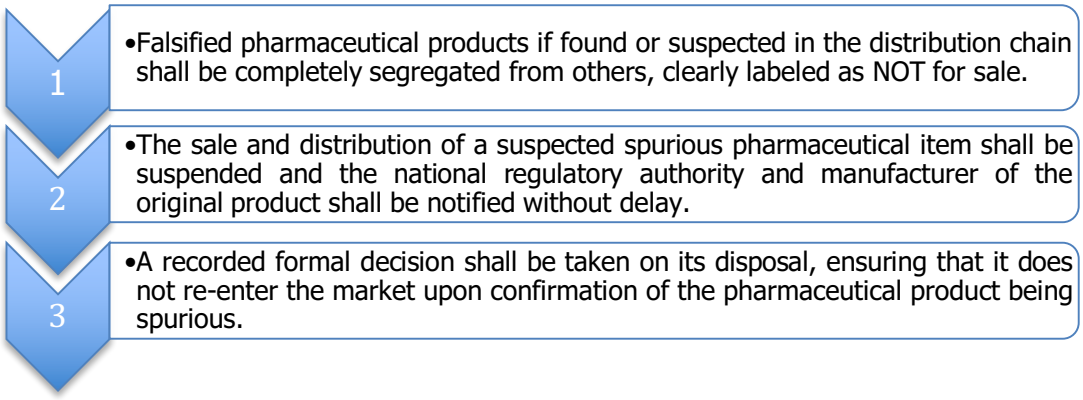
Patient groups offer support to people who seek advice and also provide educational material. However, being part of a group it is not replaceable to going to the surgery. However, it can be inferred that they are helpful in guiding and solving minor problems.

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 fake drug.

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

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



6. CONLCUSIONS

The counterfeiting of medicines is a major problem worldwide, affecting all countries in different ways. Unfortunately, it is not sufficient to solve the illegal transit of modified drugs, but it is also important to ensure that patients do not lose faith in the benefits of the medicines and follow the treatment properly. The growth of the internet and the increasing difficulty to monitor suppliers has lead to an exponentially higher proportion of consumers purchasing non genuine drugs. Definitely, nationally and internationally harmonization to define falsified medicine is needed requiring excellent coordination, to ensure a good performance, control and competent search of imitations.

Drug adulteration is a problem with different effects everywhere. It is quite complex to measure the actual extent of the dilemma and its real impact, especially in developing countries (Africa, Asia and Latin America) where the replicas' percentage is higher. This also goes hand in hand with the increase in intermediaries and non-existent regulations which expand the illegal trade.

Another cause of the proliferation of this market is the price difference of some countries to others, because the lack of regulation either does not have adequate reimbursement plans and encourages the patient to look for cheaper and easily accessible alternatives, for instance on the Internet.

It should be noted that the harmful consequences in human health, show that the risk is not so hypothetical. The possibility of taking counterfeit medications is proportional to the amount of unlawful drugs. It is extremely difficult to detect the cause of the disease if there are doubts about having eaten a manipulated medicine. For this reason, medical doctors have a pivotal role to curb and prevent the phenomenon, especially in older people, since many of them are polymedicated and may suffer more drug interactions. On the other hand, it should be remembered that fraudulent drug consumption represents more economic expenses for public health due to increased hospital admissions. Certainly it is necessary to provide more information to patients and healthcare professionals about the risks that entails the consumption of this type of drugs.

In a nutshell, it can be assumed that the adulterated drugs must follow a continuous study to be found, report, and withdraw from the market. On this basis, it should be highlighted the meaningful benefits of serialization, beyond fulfilling its essential function. The main advantage associated to this, is to provide a greater drug security so that it reaches patients in an integral manner and guarantee the laboratories supply. Similarly, it is to be distinguished the new labeling influence that do have on the reduction of products withdrawn from the market. In general, the technological processes of validation and controls of containers will improve, therefore errors will be reduced drastically. Other strengths to illustrate will be having a wider visibility of the products, as well as the speed of withdrawal of those already placed on the market. In parallel, it can be observed an upgrade in the control of the expiry date and storage containers. On the other hand, a remarkable point will be the disappearance of the coupon seal in the near future, as it has happened in the case of France, to a better refund. This will be possible thanks to the 2D code that will include more information such as the product code, batch number, expiry date and the serial number.

The patient's safety is certainly the main benefit, but so is the protection of the commercial firm. The advertising associated with any incidence of counterfeiting creates a strong threat endangering even the reputation of the most powerful brands. So much so, that new guidelines on good distribution practice are far more detailed, with stricter requirements on management of suppliers and customers quality control system. A quite helpful fact for the security and transparency of the distribution chain entities. Talking about the economic issue, Farmaindustria will make a great investment with the expectation that they will later recover the benefits of eliminating fakes. Regrettably the new strategy will be implemented late in Spain for Institutions structuring process reasons.

Although our society is experiencing a greater awareness of the harmful effects that involve the intake of an imitation drug, there is still much work to do and a higher effort is required in terms of cooperation and collaboration among Governments and organizations to be successful. So it is a general aim that all pharmacists learn about the existing challenge, since they are the final members of the supply chain. Also it is vitally important to improve their professional skills in the fight against the falsified drugs. Ultimately, this review reflects the social impact of the trouble, trying to provoke a reaction in the reader about precaution of everything what is purchased and the future changes that will arise from this new regulation, making Spain not only a safer, but also more modern, efficient and competitive sector.

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ANNEX: AECOC GS1 SPAIN HEALTH SECTOR MANAGER MÓNICA SOLER INTERVIEW

Talking about the implementation of the new standards in the verification system with the responsible of the Asociación Española de Codificación Comercial in healthcare, Mónica Soler.

QUESTION: The pharmaceutical industry will be forced to introduce systems of traceability in the production and supply of drugs. How has come so far? Could you let us in history and explain the reasons that have motivated this change in standards?

ANSWER: New regulations are due to have recently detected an alarming increase of counterfeit medicines in some countries of the European Union seriously endangering the health of patients, as well as other repercussions for the chain of the sector agents. Aspects such as the lack of transparency in the chain of distribution, the intervention of agents not regulated or subjected to more lax controls, the existence of non-traceable operations together with a supply chain complex, have favored the entry of counterfeit legal distribution channel and on the internet.

Facing this new scenario, the risk management in the manufacture and distribution of drugs by various health authorities has needed a review primarily in three areas: the identification and assessment of problems, the implementation of new measures of risk management and the review of their effectiveness.

QUESTION: Where will seal coupon information be if this is deleted, as for instance the reduced contribution?

ANSWER: The Directive does not aim the refund but verification of medicines. If it is true that, with the new system of identification, "could" the current coupon seal be replaced (something already made in France), currently do not have the necessary functions in the repository or in the database of the autonomous communities.

QUESTION: Could the identification of UI also be used to keep track of the expiry date? Or the process will be limited to verifying whether the packaging is original or fake?

ANSWER: Indeed, one of the attributes required within the UI is the expiration date. Currently the linear barcode (EAN 13) drugs only allows to automatically capture the static product information, but not the variables of production as the batch or the revocation can only be managed manually. In future drug identification system contemplates all this information within the GS1 Datamatrix two dimensional symbology encoding, capture and manage the expiration automatically.

QUESTION: What readers should use the pharmacies to identify drugs during the period of coexistence between the current model and the new?

ANSWER: Current readers must be replaced with two-dimensional code readers (are a camera). These readers are capable of reading the two types of 1 d and 2D codes.

QUESTION: Do the rules on the safety features also apply to veterinary medicinal products?

ANSWER: No. The rules apply only to medicinal products for human use.

QUESTION: Does an obligation to bear "the safety features" imply an obligation to bear both a unique identifier and an anti-tampering device?

ANSWER: Yes.

QUESTION: Once regulation (EU) 2016/161 applies, can manufacturers place the safety features, on a voluntary basis, on products not required to bear the safety features?

ANSWER: No. Once Regulation (EU) 2016/161 applies, manufacturers cannot place the safety features on medicinal products not required to bear the safety features, unless the Member States have extended the scope of application of the unique identifier or of the anti-tampering device to those medicinal products in accordance with Article 54a (5) of Directive 2001/83/EC.

QUESTION: Certain medicinal products are currently bearing an anti-tampering device on a voluntary basis. are those products allowed to maintain the anti-tampering device once regulation (EU) nº 2016/161 applies, if they are not required to bear the safety features?

ANSWER: Once Regulation (EU) 2016/161 applies, medicinal products can only bear an anti-tampering device if they are in the scope of Article 54.a.(1) of Directive 2001/83/EC for instance if they are medicinal products subject to prescription or medicinal products listed in Annex II of Regulation (EU) 2016/161 or if the Member State(s) where they are placed on the market extended the scope of the anti-tampering device to those medicinal products.

QUESTION: Would it be possible to include, on a voluntary basis, a two-dimensional barcode on the packaging of medicinal products not having to bear the safety features if the information carried by the barcode does not serve the purposes of identification and authentication of the product and does not include a unique identifier?

ANSWER: Yes, provided that the relevant labelling provisions of Title V of Directive 20014/83/EC are complied with. Examples may include two-dimensional barcodes encoding price indications, reimbursement conditions, etc.

QUESTION: Is it compulsory to print the national reimbursement number in human-readable format?

ANSWER: No. The national reimbursement number or other national number should be printed in human readable format only if required by the national competent authorities of the relevant Member State and not printed elsewhere on the packaging. It should be printed adjacent to the two-dimensional barcode if the dimensions of the packaging allow it. However, it should be in a readable format the GTIN code and the serial number.

QUESTION: How should the unique identifier be decommissioned if the two-dimensional barcode is unreadable or deteriorated?

ANSWER: The unique identifier in human readable format should be recorded by any suitable method allowing the subsequent manual querying of the repository system in order to verify and decommission the unique identifier.

QUESTION: When the barcode carrying the unique identifier cannot be read, or the verification of the unique identifier is temporarily impeded, is it possible to supply the medicinal product to the public?

ANSWER: Article 30 of Regulation (EU) Nº 2016/161 prohibits supply to the public if there is reason to believe that the packaging of the medicinal product has been tampered with, or the verification of the safety features of the medicinal product indicates that the product may not be authentic. In all other cases, the supply of medicinal products to the public is regulated by national legislation.
Without prejudice to national legislation, in the case where it is permanently impossible to read the unique identifier and verify the authenticity of the medicinal product, for example because both the data matrix and the human readable code are damaged, it is recommended that the medicinal product is not supplied to the public.

QUESTION: Can a medicinal product which cannot be authenticated be returned, and to whom? who should pay for the return?

ANSWER: It should be noted that Regulation (EU) 2016/161 does not change the national provisions in place regulating returns of medicines from pharmacies and hospitals. The regulation of returns of medicinal products, including their financial aspects, remains a national competence.

QUESTION: Will the implementation of the system drug verification have any impact on the actual cost of these, since the pharmaceutical industry must carry with all costs?

ANSWER: The cost of implementation of the directive will not have any impact on prices of medicines. The responsibility lies with industry to improve the system of verification as well as the health of their patients to fight against counterfeiting.

QUESTION: Currently, what is its degree of implementation in Spain and in the rest of the EU Member States?

ANSWER: Since the publication of the European Directive 2011/62 of the European Parliament and the Council and the executive regulation 2016/161 laying down detailed provisions relating to the packaging of the medicinal products for human use safety devices, was up countdown to its adoption by member countries. In this sense, last April 19, the Spanish Agency of medicines and health products published the draft Ministerial order which regulates those aspects that the delegate rules were left to the power of the States member. One of these aspects is the definition of the characteristics and technical specifications of the unique identifier of the drugs, still pending resolution.

From Aecoc - GS1 Spain have provided information and support to the Aemps and agents of the chain on the different options offered by the standard based on the provisions of the directive and to the needs of the Spanish market (including national code), recommending an approximation as harmonized as possible enabling interoperability in the various Member States.

QUESTION: And in other countries?

ANSWER: In other countries of the EU as France, and others such as Turkey, already have pre-existing measures on traceability of medicines based on GS1 standards. Others, such as Belgium, Italy and Greece used their own identification systems and the deadline to comply with the directive will be deferred until 2025. On the other hand, the Nordic countries (Norway, Finland, Denmark, Sweden and Iceland) that currently use a standard-compliant identification system, have recently announced the migration to the global standard of GS1, which will be effective 100% starting from 2018. This is excellent news which we hope will sow the way for many other countries of the European Union towards global harmonization.

QUESTION: What applications will allow the new system?

ANSWER: The new system is designed to accommodate the information required by the directive of all medicinal products placed on the European market in order to verify its authenticity and integrity throughout the supply chain. Once verification of the safety devices, where the unique identifier will be disabled. In addition to this functionality, you can also use for the calculation of the refund due for pharmacies to pharmaceutical companies and entities of distribution in those dispensed drugs out of the national health system, according to recently said the Director general of the Sevem.

QUESTION: How do you rate the recent adoption of the regulation of the EU on anti-tampering devices and the unique identifier?

ANSWER: We are experiencing an especially intense time in overregulation in this sector and it is a trend that affects all types of products. The adoption of these regulations is to GS1 a breakthrough in favor of standardization in the identification of medical devices. The fact that approved regulations provides for the use of the GS1 Global standards in the European context will allow to create a harmonized framework in which, as in the scene of drugs, improve patient safety and supply chain traceability.

QUESTION: What valuation does you have for the four decades of the existence of Aecoc?

ANSWER: Aecoc was born in 1977 thanks to the collaborative project of a small group of manufacturers and distributors who, with the support of some associations, decided to join forces and establish a "common language" that would lead to the introduction into Spain of the barcode. This identification system, universal today, it became a key element for trade and modern industry since it allowed to automate processes that until then were manual, providing significant advantages both for companies and for the consumer. Currently, over 27,000 companies identify their products with bar codes and, within these, companies in the health sector play an important role in the partnership, coming to represent around 3.5% of the total.