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# Máster en Evaluación y Desarrollo de Medicamentos

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Serialización de medicamentos

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## **ACRONYMS:**

**AASs:** Androgenic Anabolic Steroids.

**ACM:** Anti-Counterfeiting Measures.

**AEMPS:** Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines and Sanitary Products).

**AIFA:** Agenzia Italiana del F armaco (Italian Medicines Agency).

**ANMAT:** Administraci n Nacional de Medicamentos, Alimentos y Tecnolog a M dica (Medicines, Food and Medical Technology National Administration).

**ANVISA:** Ag ncia Nacional de Vigil ncia Sanit ria (National Sanitary Vigilance Agency).

**API:** Active Pharmaceutical Ingredient.

**CNS:** Central Nervous System.

**CCPCJ:** Commission on Crime Prevention and Criminal Justice.

**DR:** Directional Reflectance.

**EMA:** European Medicines Agency.

**FDA:** Food and Drug Administration, United States of America.

**GC:** Guardia Civil.

**GMP:** Good Manufacturing Practices.

**GTIN:** Global Trade Item Number.

**HSA:** Health Sciences Authority, Singapore.

**ICPO/INTERPOL:** International Criminal Police Organization.

**IFPMA:** International Federation of Pharmaceutical Manufacturers and Associations.

**IMPACT:** International Medical Products Anti-Counterfeiting Taskforce.

**INCB:** International Narcotics Control Board.

**IRACM:** Institute of Research against Counterfeiting Medicines.

**IUM/UMI:** Identificador  nico de Medicamento/Unique Medicine Identifier.

**LSC:** Legitimate Supply Chain.

**PFIPC:** Permanent Forum on International Pharmaceutical Crime.

**PMMA:** Polymethyl Methacrylate.

**PSI:** Pharmaceutical Security Institute.

**PSI CIS:** Pharmaceutical Security Institute Counterfeit Incident System.

**RFID:** Radio Frequency Identification.

**SEVeM:** Sistema Espa ol de Verificaci n de Medicamentos (Spanish Medicines Verification System).

**SNCM:** Sistema Nacional de Control de Medicamentos (National Medicines Tracking System).

**UN:** United Nations.

**UNODC:** United Nations Office of Drugs and Crime.

**WCO:** World Customs Organization.

**WGEO:** HMA Working Group of Enforcement Officers.

**WHO:** World Health Organization.

**WIPO:** World Intellectual Property Organization.



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## Serialization of medicines

### Abstract

The counterfeiting of medicines is a serious health concern worldwide, as it causes the loss of 200 000 to 1 000 000 people a year. Besides, it also affects societies by hampering their welfare states, as violation of property rights and tax revenues cause the loss of hundreds of direct and indirect jobs created by the pharmaceutical industry. Hence, given this scenario, local governments, as well as international organizations, such as the World Health Organization or the United Nations, have focused on carrying out strategies to counteract counterfeiting, both in developed and developing countries, as regardless of how monitored the legitimate supply chain within one country is, no country or pharmaceutical form is safe of being targeted by counterfeiting criminals. Thus, in this dissertation I sought to deliver an updated overview of the problem, focusing on the legislation being put into force in the three traditional pharmaceutical blocks, that is, the United States of America, Europe and Japan. Attention was also dragged to Argentina, Brazil and Italy, as their legislations came into force earlier than Europe's Directive 2011/62/EU, which did so on February 9, 2019.

**Keywords:** counterfeit medicines, serialization, legislation, Europe, United States of America, Spain.

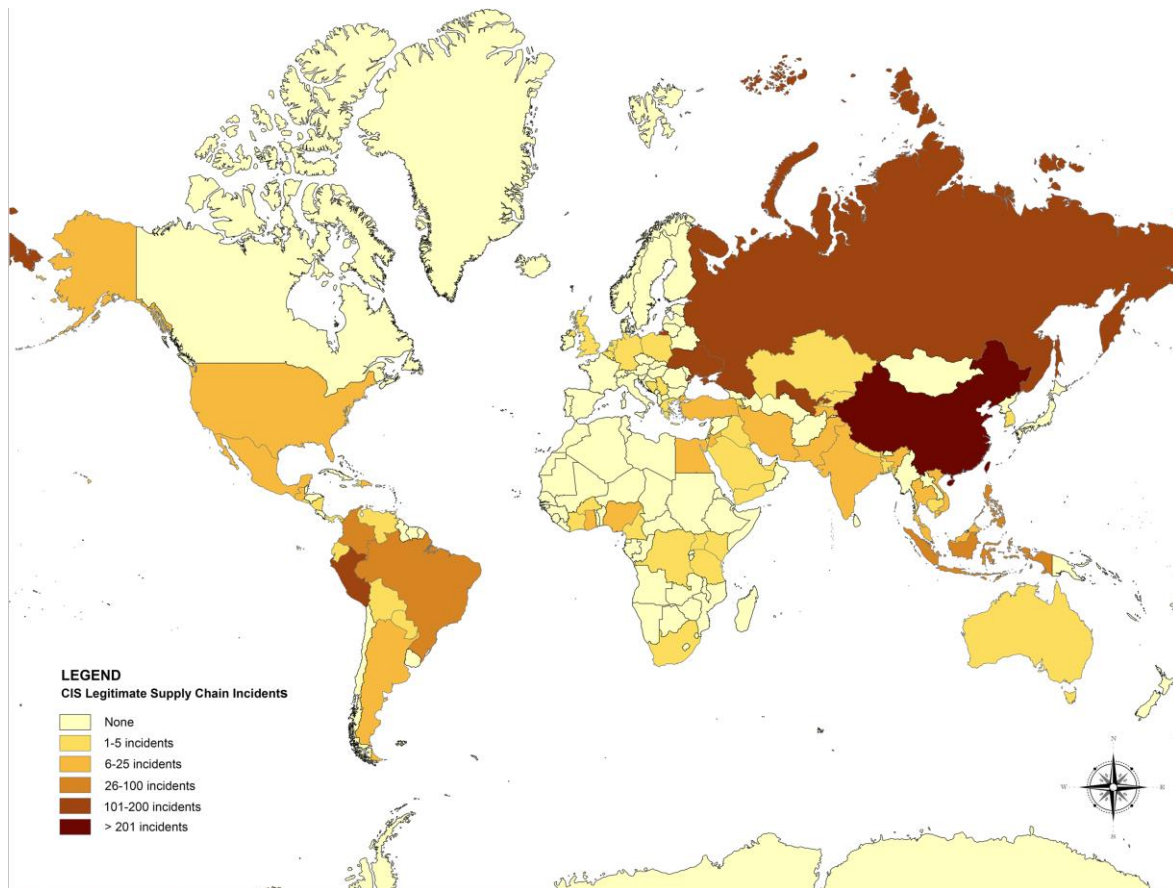


## **1 Introduction**

Counterfeit medicines, which can include products with bona fide ingredients, with sufficient or excessive quantities, products with the wrong ingredients, or products with deceptive packaging or falsely documented, may seriously threaten the health and life of patients (1) as they bypass the safeguard measures placed upon legitimate pharmaceuticals before being formally approved for the public. It has even been estimated that the risk of taking counterfeit drugs is now greater than the probability of dying from malaria and AIDS combined (2); causing the loss of 200 000 to 1 000 000 people a year (3). In addition to that, the sale of products such as these violates intellectual property rights (4) and tax revenues (5), and can lead to loss of public confidence in both medicine and public health, as well as undermine the reputation of drug companies, which might become hesitant to announce incidents of counterfeiting of their products (6).

The sale of counterfeit medicines, which do not come from an original manufacturer, or that have undergone illegal changes before reaching the consumer (7), has lately experienced an increase, both in developing and developed countries, for both brand and generic name pharmaceuticals, due to an increase in the availability of drugs, especially because of the possibility of acquiring them online, where patients are bombarded with a large number of advertisements offering lower prices than physical pharmacies and even ‘discounts’ for customers (8). Nonetheless, whereas the latter is true for industrialized countries, the reality in developing countries from Africa, some parts of Asia and Latin America is quite different, where drugs are accessible from retail stores. Anyhow, the drug formulation which is more vulnerable to counterfeiting is a tablet (9); although biotechnology drugs have also been targeted, as discussed on (3).

Some sources declare that counterfeit medicines account for around 10% of the world’s pharmaceutical market, up-scaling to 30% in developing countries (10), whereas others state that the proportions range from 1% in industrialized countries to as high as 60% in some developing countries. All in all, the World Health Organisation (WHO) has become less definite in estimating the scope of the problem in recent times as ‘*there is little validated evidence to underpin the estimations*’ (8), given that reports of counterfeit medicine detection are often based on journalistic discovery rather than on results of public health surveillance systems (11). Nevertheless, it is worldwide known that the size of the market is inversely proportional to the amount of regulation (4) (**Figure 1**).



**Figure 1. Global map of Counterfeit Incidents by country.** Pharmaceutical Security Institute Counterfeit Incident System (PIS CIS) report on counterfeited products found within the legitimate supply chain. Darker colours represent countries where the most number of counterfeiters have been found; whereas lighter colours stand for the least number or even none. Obtained from Mackey, TM *et al.* (2015).

This problem however is not a new topic whatsoever. For instance, it has been stated that ever since quinine was discovered to treat malaria on the 19<sup>th</sup> century, drug counterfeiting has been a thing as it is an extremely lucrative business, which has remained poorly policed for so long. Interpol has tried ever since creating its pharmaceutical crime unit in 2005 to tackle this problem (12), as well as the WHO, which in 2006 created a global coalition of stakeholders called International Medical Products Anti-Counterfeiting Taskforce (IMPACT) (4). IMPACT encompasses collaboration between patients, health care providers, industry, and local and government organizations (13) to build coordinated networks across and between countries in order to halt the production, trading, and selling of fake medicines around the globe (4). The same holds true for the European Council, that set up the international convention Medicrime, which is open to member countries and prosecutes those involved with counterfeit medicines through different projects, such as the one named ‘Track & Trace’ (13).

A variety of anti-counterfeiting technologies are available nowadays. Nevertheless, given the increasing technical competency of counterfeiters, traditional Anti-Counterfeiting Measures (ACM) like holograms, breakable caps and even bar codes are losing their effectiveness, leading thus to the necessity of new advanced technology (14), which should be hard to duplicate, easy to prepare, have a high throughput, be convenient to recognize and inexpensive (15) such as Radio Frequency Identification (RFID), or mass serialisation and e-pedigree (14).

Hence, because in the past decade the number of countries reporting falsified medicines has increased to pandemic proportions (12), the European Parliament sought to deal with this alarming increase within its borders by publishing Directive 2011/62/EU, which amended Directive 2001/83/EC and was transposed by the Member States in January 2013 (5). It states that *'there is an alarming increase of medicinal products detected in the Union which are falsified in relation to their identity, history or source'* (16).

Hopes are placed upon this new Directive to minimise opportunities for counterfeiters and diverters to infiltrate counterfeit supplies through the soft-entry points of a nation's drug supply chain, namely the intermediaries of the supply chain, such as wholesalers or retailers. An effective track-and-trace would not just control proliferation of counterfeiting in pharmacy supply chain, but will also enhance consumer's confidence on the firms' products (14).

## **2 Objectives**

As a consequence of all aspects related to dealing with falsified, stretched, filled, or faked drugs, which are a health problem worldwide (17), this MSc's dissertation sought to primarily provide an updated overview on the topic, as proposed by the World Health Organisation, of 'substandard/spurious/falsely labelled/falsified/counterfeit drugs' (13) given the recent entry into force (February 9, 2019) of Directive 2011/62/EU of the European Parliament and of the Council. Thus, due to the importance of providing patients with pharmaceutical products from whose legitimate origin is known, for the reaching of the general objective, the following secondary objectives had to be met:

- a) Have a general knowledge of the main international bodies that take part within the frame, whether governmental or not;

- b) Review Directive 2011/62/EU, and related legislation, to gain an insight on the frame with which the pharmaceutical industry will be legislated herein;
- c) Present the different measures applied, or planned to be applied, on the three traditional major pharmaceutical areas (United States of America, Europe and Japan), as well as other countries whose measures result attracting to the author;
- d) Report counterfeiting cases that have been tackled in Spain;
- e) List the different technological measures that have been, or could be, applied for counteracting the counterfeiting of medicines;
- f) Highlight the security placed, or planned to be applied, upon the pharmaceutical supply chain.

### **3 Methods**

Having gained a general insight overview on the topic of counterfeit drugs thanks to the recommended reading of ‘*MEDICAMENTOS FALSIFICADOS. Todo lo que debemos saber*’ (18), suggested by my supervisor, Mr. Seeger, and hence having decided how to organise this MSc’s dissertation, a literature review was carried out. Thus, this comprehensive review of the available literature was based on a search of online databases Web of Science, ScienceDirect and PubMed, being the keywords introduced for the search *counterfeit drugs* and *counterfeit medicines*. The results were narrowed down in all cases by the application of different filters, namely type of document (*article or news or review*) and date (from 2014 to date). Language restriction was applied; manuscripts written in English, French and Portuguese were reviewed, whereas all articles written in Chinese, German, Japanese and Russian were turned down. Only access to free resources, and those whose access is guaranteed by the University of Salamanca, were used (**Table 1**).

Moreover, given the special characteristics of this dissertation, the websites of the principal national and international as well as non-governmental organisations were reviewed so that up-to-date information could be gathered. Besides, the principal legislation within Europe, Spain, United States and Japan was revised, as well as that concerning other countries that were deemed interesting, namely Argentina, Brazil, and Italy.

**Table 1. Literature review.** Only those resources that were downloaded and read through are represented on this chart.

Source	Selected for revision	Included as references within this dissertation
Web of Science	32	23
ScienceDirect	17	5
PubMed	11	4
Ministry of Health and National Drug Agencies websites	11	7
Law Enforcement Corporations	3	2

## **4 Results**

### **4.1 The problem of counterfeiting**

Counterfeit goods, which are defined as ‘*any commodity, including its packaging, which carries without authorization an identical trademark or which does not differ in its essential aspects from a registered product or service trademark registered for the same type of goods and which, for that reason, violates the rights of the trademark owner; any symbol of a product or service trademark (including logo, label, self-adhesive, brochure, instructions for use or warranty bearing such a symbol), even if presented separately; any packaging bearing counterfeit trademarks*’ (5), stretch to nearly every product on the market and have often led to considerable harm to consumers, including death. Counterfeiting, together with piracy, costs just US businesses an estimated figure of \$200 billion a year, as well as the loss of more than 750 000 jobs. Besides, due to violation of intellectual property rights, namely copyrights, trademarks, and patents, inventors (as well as artists, musicians, and authors) might be discouraged to innovate as a result of widespread theft associated with counterfeiting and trafficking of pirated goods, which in the end will be a drawback for society as a whole, as intellectual property protections provide the ability to prosper, and create jobs and products that enrich consumers’ lives (19).

Nevertheless, the biggest problem regarding the sale of counterfeit goods is that consumers remain both the root problem and the ultimate destination (20); whether they buy fake goods on purpose or are simply misled towards doing it (14). As discussed in reference (20), it is not clear whether demographic differences, namely economic status, generate

variations between groups in adopting a certain ethical behaviour towards purchasing counterfeit goods, as there are authors who declare that low-income households hold more favourable attitudes towards the purchase of counterfeiters, whereas others state that income has no significant effect on consumers' intention to purchase counterfeit goods. As conclusion, they suggest that industry and policy-makers need to understand why some consumers buy counterfeiters.

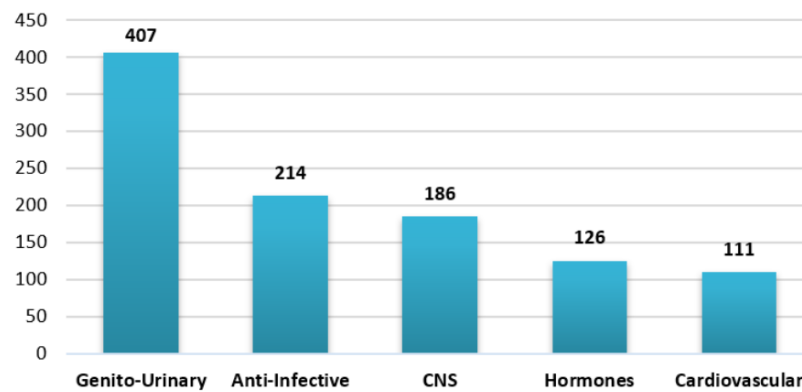
#### 4.1.1 The counterfeiting of drugs

Out of all possible counterfeit activities, counterfeiting drugs is perhaps among the most profitable (profits of around 3000%; a margin that is 10 times bigger than the profit rate of trafficking heroin (19)), as prosecution of these crimes has been so infrequent (12), with illegal operations that escape detection (4), and extradition so rare, that the downside risk of counterfeiting is low (12). Thus, meanwhile the punishment for buying 1 kilo of cocaine would be a minimum of 5 years to a maximum of 40 years in jail, the punishment for buying 1 kilo of sildenafil is typically 3 years (4). Moreover, because criminals are aware of standard quality testing protocols, they have improved over the years the former poor imitation products to genuine- and trustworthy-appearing ones (21).

The biggest problem regarding the sale of counterfeit pharmaceuticals is that consumers usually believe they are buying genuine products (7), which can have fatal consequences, as counterfeit drugs can include lifestyle drugs, life-saving drugs, patents/generic drugs and even medical devices (14). Any medication that is in high demand is an attractive target for counterfeiters (22); whether in developing countries, where the most counterfeited pharmaceuticals are those used to treat malaria, tuberculosis and AIDS, or in developed countries, where the most targeted products are those intended to treat erectile dysfunction, weight loss and anabolic products (10) (**Figure 2**). On top of that, detection of falsified pharmaceuticals is difficult as medical personnel might attribute the problem to poor clinical outcomes due to patient variation, and because patients may not want to reveal that they bought drugs without prescription over the Internet (19).

The detrimental health effects can be produced either by the non-treatment with the legitimate medicines or by the adverse effects caused by overdosed content or contaminations (22); being thus the possible scenarios a patient can face the following ones:





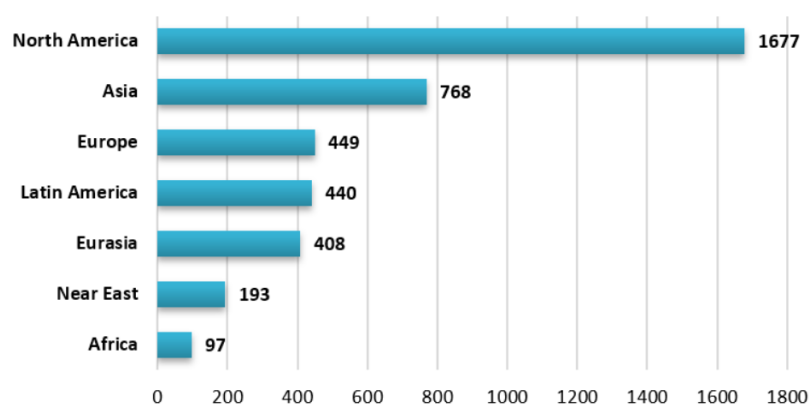
**Figure 2. Pharmaceutical Security Institute report on Counterfeit Incidents and Therapeutic Categories, 2017.** Genito-Urinary, Anti-Infective, Central Nervous System (CNS), Hormones and Cardiovascular were the five most frequently counterfeited therapeutic categories targeted worldwide in 2017. During that year, 3,509 incidents were reported, where all therapeutic categories were targeted, meaning an increase of 21% in comparison to the previous year. Screenshot acquired from [www.psi-inc.org](http://www.psi-inc.org) on January 21, 2019.

- a) A counterfeit drug has no active ingredient or no harmful ingredients. In this case, the drug fails to help the patient get better, which can ultimately harm them.
- b) A counterfeit drug has no active ingredient but does have any number of harmful ingredients (such as bacteria-laced water, floor wax, coloured dye, powdered cement, boric acid, antifreeze (19), non-purified talc, amphetamine, commercial grade paints, paracetamol, metronidazole, gly-buride (23)). Given this case, the patient will not only be prevented from getting helped to get better, but will also experience a quick reaction against the contaminants.
- c) The Active Pharmaceutical Ingredient (API) declared on the labelling is not the one that is present in the medicine. In this case, patients at higher risk will be those who, while taking any other medication, unknowingly take the counterfeiter and experience harmful interactions.
- d) A different concentration or the wrong dose of the drug is present. In this circumstances, patients might either get undertreated or overdosed (19).

In summary, the detrimental consequences can be due to the intake of the falsified medicines *per se* or due to side effects, which anyhow supposes a serious problem for society due to, among others, antibiotics resistance and/or decreased confidence in certain drugs (13).

An increase around 800% in counterfeit cases was observed worldwide between years 2000 and 2006, which caused an estimated 800 000 deaths (24). Nevertheless, and as shocking as the figure is, it should be pointed out that these figures are under-estimations as

the real figures remain undiscovered (25). For instance, the reporting of counterfeit products in Europe within just 1 year (2007 to 2008) experienced an increase by 118%. This rise brought along with it a rise of 57% on their confiscations (**Figure 3**). Thus, whereas counterfeit drugs are less than 1% of the market in industrialized countries (26), in developing countries they account for between 10% and 30% of all drugs sold (13). Criminals take advantage of certain scenarios, such as drug shortages, to introduce counterfeit drugs into the market (19), as the most counterfeited pharmaceuticals within one country are the ones that are most demanded by the population (24), namely antibiotics, antivirals and antimalarials (27).



**Figure 3. Counterfeit incidents grouped by regions of the world, 2017.** Even though the regions with more reported incidents are not necessarily those with weak enforcement and inspection programmes, and the ones with seemingly low incident are not necessarily unaffected by or at a lower risk, the truth is all regions experienced an increase in pharmaceutical crime. Screenshot acquired from [www.psi-inc.org](http://www.psi-inc.org) on January 21, 2019.

In industrialised countries however, one of the most counterfeited medicines are synthetic androgenic anabolic steroids (AASs), or simply anabolic steroids. Developed for the treatment of certain hormonal dysfunction or muscle wasting; they are nowadays used by athletes, fitness centre users and bodybuilders. The indiscriminate and inappropriate use of AASs may lead to the development of coronary diseases, hepatic and renal dysfunctions, psychiatric syndromes including aggression, violence, psychosis, and suicide, and physical effects, such as feminization in men, decreased sperm counts, and testicular atrophy; whereas women can experience masculinization, acne induction, deepening of the voice, clitoral hypertrophy, and male hair distribution patterns (7). Another very popular counterfeiter in developed countries is sildenafil, a drug that is used to treat erectile dysfunction, a problem that is increasing in incidence as men age. In an analysis of microbial loads of various illicit erectile dysfunction drugs, 23% were contaminated with more than  $10^3$  colony-forming units;

whereas legitimate pills contained none; that is, they were produced in such a way that cannot match the clean conditions of legitimate pharmaceuticals (4).

It is estimated that there are about 36 000 active internet pharmacies, of which less than 5% are thought to be legitimate. Fortunately for American (**Annex 1a**) and European (**Annex 1b**) citizens, access to a list of authorised websites is provided (28). Intervention from authorities against fake online pharmacies though is really difficult, given that websites are disconnected very quickly, transfers are made in very short periods of time (5), and because consumers seek alternative ways of acquiring the products to treat certain pathologies (4), led by the unawareness of the dangers of purchasing counterfeit drugs online and because of the embarrassment and lower costs (savings of up to 75%) (19) offered to treat certain pathologies, such as erectile dysfunction (4), or HIV-infection (13). In addition to that, some of those Internet sites are linked to terrorist groups, such as Al Qaeda, or organized crime, which poses a threat to national and international security, besides the possibility of facing other consequences, such as credit card fraud, identity theft, and computer viruses (19).

Yet even more dangerous for human health is the forging of genuine medicines, which have been discovered in counterfeited packaging to extend the expiry date or to commit a fraud against governments programmes (29); or the adulteration of herbal drugs and herbal dietary supplements, which are advertised as ‘all natural’, but may include not indicated ingredients, and even synthetic drugs with slightly modified structures which are more difficult to detect than those of the original drugs, but that remain harmful for human health (30). Part of the biggest problem with such products is that ‘natural’ advertised products are perceived by the population as no source of any risk for human health (24).

Given this current scenario, the need to identify effective anti-counterfeiting strategies has been raised as a main policy concern, which includes a) legal actions and regulations on illicit traders, b) countermeasures using technologies, c) consumer education and d) cooperation with enforcement agencies (31). Thus, by making these strategies effective, European countries (for instance) will not only be protecting the patients’ health, but will also be guaranteeing the continuity of their welfare states, which are being affected by, and not restricted to, EUR 10.2 billion each year, with 90 900 direct and indirect jobs lost annually (32).

#### 4.1.2 The counterfeiting of drugs in Spain

The competent body in Spain in regard to pharmaceutical products is the Spanish Agency of Medicines and Sanitary Products (AEMPS from its acronym in Spanish, *Agencia Española de Medicamentos y Productos Sanitarios*), which is appointed to the Ministry of Health Service, Consumption and Welfare (33).

Since 2008 the agency has developed quadrennial strategies to counteract counterfeit pharmaceuticals, being the one into effect right now the so called ‘Strategy against falsified pharmaceuticals 2016-2019’ (‘Estrategia frente a medicamentos falsificados 2016-2019’ in Spanish). In this strategy, the perspective of the problem is presented, where it is pointed out that the incidence of falsified medicines cases has increased both in Spain and Europe, although it is highlighted that no counterfeiter has reached Spanish citizens through the legal supply chain. It is also emphasised that citizens’ awareness-raising through campaigns has been proved to be one of the most effective actions towards maintaining public health. Besides, a mention to the existing debate within the EU about veterinary medicines, which are a less targeted market, is made, since they have also been found counterfeited in the illegal market. Thus, it is suggested that a possible solution to counteract these might be through a modification of Directive 2001/82/CE, the European mandate that governs the production, distribution and selling of such products (34).

On its website, the AEMPS publishes information notes related to different alerts, being the last one made public regarding falsified medicines and/or sanitary products on May 28, 2018, when it was announced that Serbian authorities had warned about the confiscation of nine counterfeited Durex prophylactic units (**Figure 4**). The legitimate units, produced by Reckitt Benckiser Healthcare Ltd, United Kingdom, are also exported to Spain, although no counterfeiter has been found in the peninsula. Regardless, the AEMPS adds some advices, namely a) carefully examine the products before use, taking into account the information must be in Spanish; b) contact the local distributor if counterfeit suspicion arises, so as to confirm the status of the product; and c) inform the AEMPS if the product is confirmed to be a counterfeiter, specifying from whom it was purchased (35).

Together with the AEMPS, the Spanish Law enforcement bodies, namely Guardia Civil (GC) and Policía Nacional, work to break up criminal organizations within the country. Thus, over 2018, 4 were the dismantling operations reported by Guardia Civil in their website:



**Figure 4. Counterfeit Durex prophylactics units.** The secondary packaging materials contained, in-between the expiry date and the batch, the words ‘Made in Thailand’ or ‘Made in China’. Image obtained from [www.aemps.gob.es](http://www.aemps.gob.es) on January 22, 2019.

- a) On April 4, 2018, the GC made public the results of the AYÚRVEDA operation, which had been triggered as a result of a police report made by an Iranian pharmaceutical company, who had been defrauded by a Spanish fraudulent laboratory based in the province of Teruel. The Arabic company had paid for some pharmaceuticals that were never delivered, which ended up with the discovery of an international criminal organization (36).
- b) 1,336 dose units were reported to be seized on April 17, 2018 in Granada. The GC arrested 10 people, and investigated another 41, for swindling the Andalusian Health Service (*Servicio Andaluz de Salud* in Spanish) by subtracting stamps from medical centres to acquire medicines in pharmacies to thereafter illegally sell them in fitness studios (37).
- c) The SUMMAS operation was reported on May 31, 2018, with two people being accused of defrauding more than EUR 1 000 000 by offering a medullar lesion treatment with cells extracted from the patients. In reality it was just therapeutic massages and homeopathic pills (38).
- d) A simultaneous operation in Toledo, Madrid and Barcelona broke up a criminal organization that had made millions of euros in profit by selling nutritional supplements adulterated with tadalafil, an API used to treat erectile dysfunction (39).

### 4.1.3 United Nations

The United Nations (UN) is an international organization that was founded in 1945. Nowadays it compiles 193 Member States, and seeks to take action on the issues that confront humanity, such as peace and security, climate change, sustainable development, human rights, terrorism, and humanitarian and health emergencies, among others (40).

#### 4.1.3.1 World Health Organization

The World Health Organization, which began when its Constitution came into force on April 7, 1948, is now present in 150 countries to direct and coordinate international health within the United Nations system. Given its importance within the global overview of health, the WHO keeps a record on up-to-date information related to it, which is published on the ‘News’ section of their website (41). Within it, one can find the section dedicated to the ‘*Substandard and falsified medical products*’, where the key facts and the definitions are gathered.

There is no international consensus regarding the definition of counterfeit medicines (13), yet the WHO defines them as ‘*medical products that deliberately/fraudulently misrepresent their identity, composition or source*’. Moreover, it also indicates that every region of the world is at risk of such medicines, and that all main therapeutic categories have been reported to WHO, including medicines, vaccines and *in vitro* diagnostic products (42).

##### 4.1.3.1.1 International Medical Products Anti-Counterfeiting Taskforce

In response to the health risk that counterfeit medical products cause to all communities, in February 2006 the WHO launched the International Medical Products Anti-Counterfeiting Taskforce (IMPACT). Such taskforce comprises all the major anti-counterfeiting players, from international to non-governmental organizations, enforcement agencies, pharmaceutical manufacturers associations, and drug and regulatory authorities, on the assumption of creating a partnership to fight these crimes.

The IMPACT handbook was published in Italy after the ‘Declaration of Rome’, and can be found online. It compiles *proposals and recommendations to be adopted through a consensus-based approach and made public*, which by any means does not commit *the participating governments, organisations, institutions, agencies and associations in any way, but rather constitutes a reference for guidelines, official policy or other action, as appropriate* (43).

#### 4.1.3.2 United Nations Office of Drugs and Crime

The UN creates offices to tackle different relevant issues according to the purposes and principles contained in its founding Chapter (40). One of those offices is the United Nations Office of Drugs and Crime; on whose website homepage (**Figure 5**) one can, by simply clicking on the different tags, access one of the several topics the office deals with: falsified medical products (44). The fact that a tag to learn more about counterfeiting medical products is accessible from the homepage highlights the importance the UN gives to the matter.

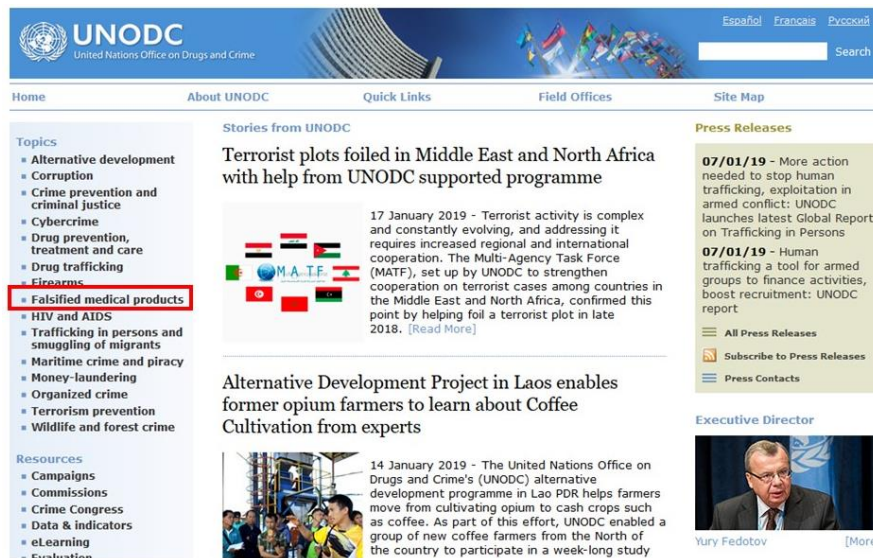
The trafficking of falsified medical products, as has been already stated, poses a public health risk; and which can be incremented given the fact that supply chain for medicines operates at a global level. Hence, *a concerted effort at the international level is required to effectively detect and combat the introduction of falsified medical products along this supply chain.*

A total of 20 sessions have been held to date by the Commission on Crime Prevention and Criminal Justice (CCPCJ), which on its last session adopted resolution 20/6 due to the concern about the involvement of organized crime in the trafficking. Besides, it highlights the importance of the cooperation between the International Narcotics Control Board (INCB), the WHO, the World Customs Organization (WCO) and the International Criminal Police Organization (ICPO/INTERPOL) with regional organizations, national regulatory agencies and even the private sector where appropriate (45).

#### 4.1.4 INTERPOL: Pharmaceutical Crime Unit

The ICPO-INTERPOL, or International Police, or simply INTERPOL (46), is the world's largest international police organization, with a record number of 194 member states (47). It was conceptualised in 1914 at the first International Criminal Police Congress, held in Monaco; although it was not established until 1923 (48). Its role is, as they gather in their website, *to enable police around the world to work together to make the world a better place.* Thus, to work on that direction, the organization counts with the help of *high-tech infrastructure of technical and operational support* (47).

In concordance with its stated role, the organisation holds a Pharmaceutical Crime Unit *to provide operational support, analysis and training to help national police to tackle widescale drug trafficking.* Drugs trafficked, as well as the routes they are being distributed



**Figure 5. United Nations Office of Drugs and Crime homepage.** The UNODC website highlights several topics on its homepage, being falsified medical products one of them. Screenshot acquired from www.unodc.org on January 19, 2019.

by, are constantly evolving, so national, regional and international law enforcement bodies need to work in a coordinated way, which is achieved with the help provided by INTERPOL in the following ways:

- a) *Global operations against drug trafficking and assistance to ongoing investigations;*
- b) *Criminal analysis of intelligence on drug trafficking routes, modus operandi and the criminal networks involved;*
- c) *Comprehensive training for police worldwide to better tackle drug trafficking* (49).

Regarding the operations coordinated by INTERPOL, there are a total of 6 named operations, although each of them may include more than just one edition:

- a) Operation Pangea was first launched on November 12, 2008 with the objective of *combating the sale of illegal medicines online*. It has been re-edited seven more times, being the last call on June 9-16, 2015. The number of participants has exponentially grown since the first edition: from 10 countries in 2008 to 115 (besides 236 agencies) in 2015. Spain joined the taskforce on its second edition on November 16-20, 2009 (50).
- b) Operation Mamba has been held in three occasions: 29 September – 5 October 2008, August 2009, and July-August 2010; with the goal of disrupting *the*



*activities of transnational organized criminals involved in the trafficking of counterfeit medical products in Eastern Africa (51).*

- c) Operation Storm targets counterfeit medicines in Southeast Asia. It has been held up to 6 times since its launch in 2008 (52).
- d) Operation Cobra aims to identify, investigate and disrupt networks involved in pharmaceutical crime such as counterfeiting, illicit production and unauthorized sales of medicines in Western-Africa. It was only held once in 2011, involving a total of 7 countries (53).
- e) Operation Giboia is a multi-country operation against pharmaceutical crime in Southern Africa. It holds two editions; one in 2013, and the other one in 2015 (54).
- f) Operation Porcupine was held twice (27-29 May and 24-26 June) in 2014. It involved 7 western African countries, as the operation worked to disrupt networks involved in pharmaceutical crime in West Africa (55).

Moreover, the organisation offers training, both on an on-the-ground intervention, as well as online, with guides available in up to six different languages (56). Besides, with the aim of counteracting the counterfeiting of medicinal products, the organisation brings together all the players that might be required to be involved: from police, customs, and health regulatory authorities, to scientists and the private sector. Thus, its main partners are: WHO, Permanent Forum on International Pharmaceutical Crime (PFIPC), Pharmaceutical Security Institute (PSI), International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Health Sciences Authority, Singapore (HAS), Council of Europe, European Commission, Institute of Research Against Counterfeiting Medicines (IRACM), UNODC, HMA Working group of Enforcement Officers (WGEO), and World Intellectual Property Organization (WIPO) (57).

#### **4.2 Legislative actions**

Fadlallah, R. *et al.* propose that changes in drug laws and legislation could contribute to an increased amount of counterfeit drugs being detected, although they need fulfilling the following criteria: a) be specific to counterfeit drugs, b) focus on public health rather than the intellectual property perspective, c) address the entire illicit online pharmacy ecosystem, d) include sufficient legal and administrative framework to criminalize fraudulent falsification, and e) be complemented by strong enforcement capacity as well as education of judges,

lawyers, and the public. This must be met by all countries, otherwise rogue online pharmacies can bypass stringent regulation by operating their websites within jurisdictions that have the least restrictive regulatory framework (6).

#### 4.2.1 Europe

As early as 2006, the Commission warned about the sale of counterfeit medicines on the Internet (5); which just 5 years afterwards lead to the publication of Directive 2011/62/EU, where falsified medicinal products are defined as ‘*any medicinal product with a false representation of:*

- (a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients;*
- (b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or*
- (c) its history, including the records and documents relating to the distribution channels’ (16).*

Hence, this European law seeks to fight, amongst many other points, the poor oversight of the drug supply chain and the dearth of international and regional partnerships between countries and non-governmental organisations (12).

##### 4.2.1.1 Directive 2011/62/EU of the European Parliament and of the Council

‘Directive 2011/62/EU of the European Parliament and of the Council’ was published on June 8, 2011 to amend ‘Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products’. Hence, this amendment came into place having regarded a total of 36 points; and from which the following are the most relevant ones for this MSc’s dissertation:

- *3: Past experience shows that such falsified medicinal products do not reach patients only through illegal means, but via the legal supply chain as well.*
- *5: A definition of ‘falsified medicinal product’ should be introduced in order to clearly distinguish falsified medicinal products from other illegal medicinal products, as well as from products infringing intellectual property rights.*

- 6: *Legislation in relation to medicinal products should address all actors in the supply chain.*
- 10: *Member States should take measures to prevent these falsified medicinal products, if introduced into the Union, from entering into circulation.*
- 11: *Safety features for medicinal products should be harmonised within the Union in order to take account of new risk profiles [...]. Those safety features should allow verification of the authenticity and identification of individual packs, and provide evidence of tampering.*
- 18: *In order to ensure a similar level of protection of human health throughout the Union, and to avoid distortions in the internal market, the harmonised principles and guidelines for inspections of manufacturers and wholesale distributors of medicinal products as well as of active substances should be strengthened.*
- 25: *The public should be assisted in identifying websites which are legally offering medicinal products for sale at a distance to the public. A common logo (**Figure 6**) should be established, which is recognisable throughout the Union, while allowing for the identification of the Member State where the person offering medicinal products for sale at a distance is established.*
- 26: *The Commission should, in cooperation with the Agency and Member States, run awareness campaigns to warn of the risks of purchasing medicinal products from illegal sources via the Internet (**Annex 2a-d**).*
- 27: *Member States should impose effective penalties for acts involving falsified medicinal products taking into account the threat to public health posed by those products (16).*



**Figure 6. European logo for the online sale of medicines.** The common logo, which consists of a national flag in the middle left side which corresponds to the EU country (plus Norway, Iceland and Liechtenstein) where the pharmacy or retailer is registered or authorised, was first introduced after the approval of Directive 2011/62/EU. It was adopted on June 24, 2014, and as of July 1, 2015, all online pharmacies or retailers legally operating in the EU must display the logo. Screenshot acquired from [www.ec.europa.eu](http://www.ec.europa.eu) on January 22, 2019.

#### 4.2.1.2 Commission Delegated Regulation (EU) 2016/161

Signed on October 2, 2015, by President Jean-Claude Juncker, the European Commission presented the regulations *supplementing Directive 2011/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use*. XI Chapters and 50 articles lay the foundations for a Union-wide consensus, although its specific content regarding *the characteristics and technical specifications of the unique identifier* (58) will be assessed further below in this MSc's dissertation.

#### 4.2.1.3 European Council: International Convention Medicrime

Treaty No.211, entitled *Council of Europe Convention on the counterfeiting of medical products and similar crimes involving threats to public health*, entered into force on January 1, 2016, after five ratifications, including at least three from member States of the Council of Europe. It is divided into XI Chapters and 33 Articles; and can be summarised as follows:

*The 'Medicrime Convention' is the first international criminal law instrument to oblige States Parties to criminalise:*

- a) the manufacturing of counterfeit medical products;*
- b) supplying, offering to supply and trafficking in counterfeit medical products;*
- c) the falsification of documents;*
- d) the unauthorised manufacturing or supplying of medicinal products and the placing on the market of medical devices which do not comply with conformity requirements* (59).

To date, the convention has been ratified by fifteen nations, and signed by another thirteen (**Annex 3**); furthermore, there are a total of four other countries (Belarus, Congo, Ivory Coast and Tunisia) that have been invited to sign the treaty. The last country to ratify the convention was Portugal, who did so on December 18, 2018. On the contrary, Spain ratified it on August 5, 2013, almost a year later after the placing of the signature on October 8, 2012 (60).

### 4.2.2 Spain

The third edition of the ‘Strategy against falsified pharmaceuticals’, published on April 11, 2016, had its guidelines slightly modified regarding the previous editions. European Directive 2011/62/EU was already known to become effective in 2019 by the time the strategy was being developed, which obliged the Spanish authorities to include new aspects. The most remarkable of those aspects are a) the co-operation required among AEMPS, the Autonomous Communities governments, the Spanish Tax Agency, the Law enforcement organizations, the pharmaceutical industry, the retailers and the pharmacies; and b) the existence of a website for Internet-users to safely check for legitimate online-operating pharmacies (**Figure 7**).

Furthermore, derived from the Medicrime convention ratification, the law enforcements applied are listed, being these a) *Real Decreto Legislativo 1/2015, de 24 de julio*, which classifies the counterfeiting of medicines (production, trading, retailing, distribution and selling) as a very strong infraction, b) *Real Decreto 782/2013, de 11 de octubre*, about medicines distribution for human use, c) *Real Decreto 870/2013, de 8 de noviembre*, through which the online sale of medicines for human use without medical prescription is regulated, and d) the Penal Code modification on the articles related to crimes against public health, and in particular the ones related to medicines (articles 361, 362, 362 bis, 362 ter, 362 quarter and 362 quinquies) (34).



**Figure 7. AEMPS interactive map website screenshot.** This interactive political map allows the internet-user to find out which are the pharmacies legally operating online. Screenshot acquired from [distafarma.aemps.es](http://distafarma.aemps.es) on January 22, 2019.

The AEMPS holds as well on its website links to two public awareness-raising campaigns (**Annex 4a**); one of its own and another one from the UNODC (61). The ‘Do not buy counterfeit medicines over the internet. It can be lethal for your health’ campaign (**Annex 4b-d**), promoted by both the AEMPS itself and the former Ministry of Health, Social Services and Equality, warns about the risks one can face when consuming fake pharmaceuticals, given that unlike other fake products, rogue medicines have a direct impact on one’s health. Furthermore, it offers advices to recognise fraudulent online pharmacies, highlighting that besides acquiring harmful products, personal data is at risk as well when purchasing from e-commerces such as these (62).

#### 4.2.3 United States of America

The Food and Drug Administration (FDA) is the governor body in charge of guaranteeing that pharmaceuticals are safe and effective. Its duties however are becoming more and more difficult to be accomplished, as patients bypass traditional sources of medication and purchase drugs from rogue Internet pharmacies that pose as legitimate businesses (19). For the latter, the FDA has launched public education campaigns through magazine public service announcements, education leaflets, news articles, a consumer website ([www.fda.gov/counterfeit](http://www.fda.gov/counterfeit)), and a pharmacist education programme (4); that together with the Counterfeit Drug Task Force is fighting to counteract counterfeiting both in the United States and worldwide. Some of these strategies include the use of technology and regulatory security practices to create rapid response systems, although poorer countries, where the problem is bigger, often lack the resources to apply them (13).

In 2003 in Florida, the *Prescription Drug Protection Act* was billed as the toughest anti-counterfeit drug wholesale in the country. It imposed an important number of credentialing requirements and the use of pedigree papers for all prescription drugs subject to wholesaling or dispensing within the State. Nevertheless, this law was victim to several loopholes, such as the fact that only 34 drugs were registered for pedigree paper use, and whose authenticity, on top of that, could not be proved (6). Regardless, this laid the foundations for the *Drug Quality and Security Act* signed to law by President Obama on November 28, 2013, and which provides for a national-wide track-and-trace system to allow the monitoring of drugs from their manufacturer to the pharmacy (19).

*Public Law 113-54–November 27, 2013*, on its second title, which may be cited as *Drug Supply Chain Security Act*, amends *Chapter V (21 U.S.C. 351 et seq.)* by adding at the

end *Subchapter H–Pharmaceutical Distribution Supply Chain*, which is composed of 11 sections, from which the following ones stand out for the purpose of this MSc’s dissertation:

**Sec. 581. DEFINITIONS.** From the 29 definitions gathered on this Act, the following shall be highlighted:

(8) *ILLEGITIMATE PRODUCT.*—*The term ‘illegitimate product’ means a product for which credible evidence shows that the product—*

*‘(A) is counterfeit, diverted, or stolen;*

*‘(B) is intentionally adulterated such that the product would result in serious adverse health consequences or death to humans;*

*‘(C) is the subject of a fraudulent transaction; or*

*‘(D) appears otherwise unfit for distribution such that the product would be reasonably likely to result in serious adverse health consequences or death to humans.*

(14) *PRODUCT IDENTIFIER.*—*The term ‘product identifier’ means a standardized graphic that includes, in both human-readable form and on a machine-readable data carrier that conforms to the standards developed by a widely recognized international standards development organization, the standardized numerical identifier, lot number, and expiration date of the product.*

(15) *STANDARDIZED NUMERICAL IDENTIFIER.*—*The term ‘standardized numerical identifier’ means a set of numbers or characters used to uniquely identify each package or homogenous case that is composed of the National Drug Code that corresponds to the specific product (including the particular package configuration) combined with a unique alphanumeric serial number of up to 20 characters.*

(25) *TRANSACTION HISTORY.*—*The term ‘transaction history’ means a statement in paper or electronic form, including the transaction information for each prior transaction going back to the manufacturer of the product.*

(27) *TRANSACTION STATEMENT.*—*The ‘transaction statement’ is a statement, in paper or electronic form, that the entity transferring ownership in a transaction—*

*'(A) is authorized as required under the Drug Supply Chain Security Act;*

*'(B) received the product from a person that is authorized as required under the Drug Supply Chain Security Act;*

*(C) received transaction information and a transaction statement from the prior owner of the product [...];*

*(D) did not knowingly ship a suspect or illegitimate product;*

*(E) had systems and processes in place to comply with verification requirements [...];*

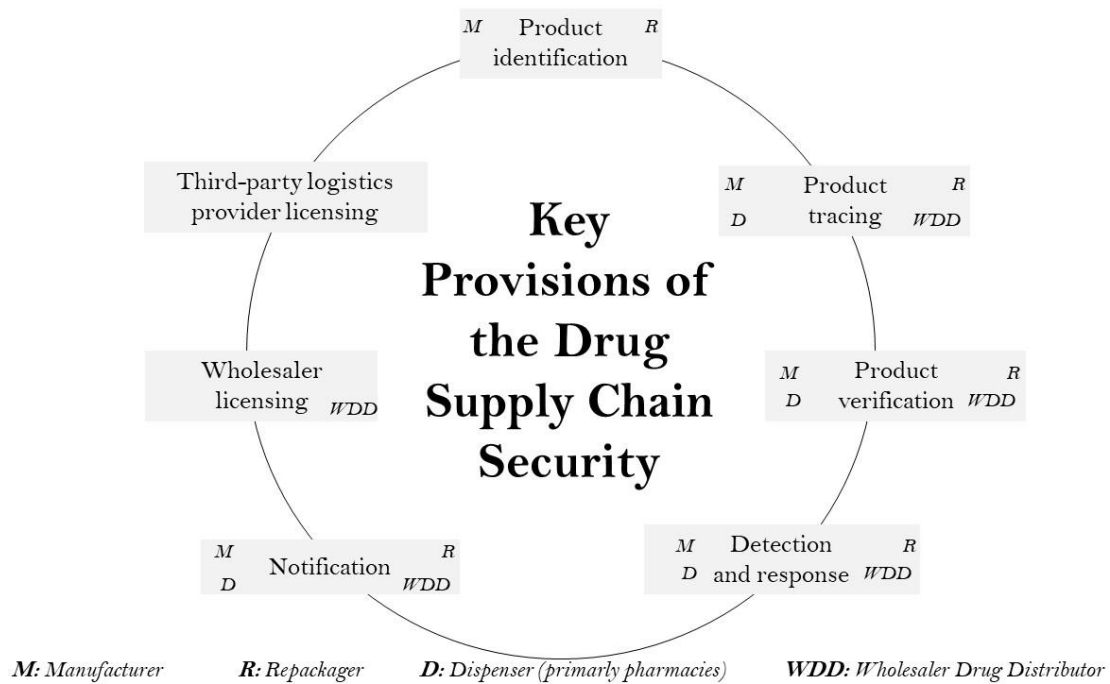
*(F) did not knowingly provide false transaction information; and*

*(G) did not knowingly alter the transaction history.*

**Sec. 582. REQUIREMENTS.** It is stated that *each manufacturer, repackager, wholesale distributor, and dispenser shall comply with the requirements set forth in this section with respect to the role of such manufacturer, repackager, wholesale distributor, or dispenser in a transaction involving product.* Moreover, it clarifies that should any entity meet the definition of more than one of the entities, *such entity shall comply with all applicable requirements in this section, but shall not be required to duplicate requirements (Figure 8).*

**Sec. 203. ENHANCED DRUG DISTRIBUTION SECURITY.** It is established that in 10 years from the enactment of the Drug Supply Chain Security Act (November 27, 2023), *interoperable, electronic tracing of product at the package level requirements shall go into effect.* That is, a) transaction information and transaction statements, b) product identifier at the package level for each package included in the transaction, and c) systems and processes for verification of product at the package level. Besides, it is also stated the necessity of creation of guidance documents by the Secretary to a) aid trading partners in the identification of suspect product and notification termination, and b) outline and make recommendations with respect to the system attributes necessary to enable secure tracing at the package level, so as to infer the contents of a case, pallet, tote or other aggregate of individual packages (63). Such guidance documents can be found at [www.fda.gov](http://www.fda.gov) (64).





**Figure 8. Key Provisions of the Drug Supply Chain Security.** Should all parties fulfil their duties, the Supply Chain will be secured against illegitimate products, whatever their origin. Information extracted from [www.fda.gov](http://www.fda.gov) on February 18, 2019.

One of the above mentioned campaigns run by the FDA to inform patients is the so-called ‘6 Tip-offs to Rip-offs: Don’t Fall for Health Fraud’ (65). This campaign seeks to set forth why one should be suspicious when coming by health products that claim ‘*miracle cure*’, ‘*revolutionary scientific breakthrough*’, or ‘*alternative to drugs or surgery*’, offering the reader 6 tip-offs to help you identify rip-offs, as well as advice to ask doctors or any other health care professional before acquiring any suspicious product:

- a) Be suspicious of one-product-does-it-all offers. Very few drugs are capable of treating more than one condition at a time.
- b) Personal testimonials proving success can be easily scammed and cannot substitute scientific evidence by any means.
- c) Escape from quick-fixers. Not even legitimate products can treat conditions quickly.
- d) ‘All natural’ advertised products have been found not so natural by the FDA; containing *high doses of prescription drug ingredients or even untested active artificial ingredients*. Regardless, even naturally produced ingredients can kill when consumed, such as some poisonous mushrooms.
- e) ‘Miracle cures’, ‘new discoveries’, ‘scientific breakthroughs’ or ‘secret ingredients’ are just attention-seekers. *If a real cure for a serious disease were*

*discovered, it would be widely reported through the media and prescribed by health professionals.*

- f) Claims like *‘The pharmaceutical industry and the government are working together to hide information about a miracle cure’* are baits to distract consumers from the obvious, common-sense questions about the so-called miracle cure.

Besides, consumers are offered the possibility of subscribing to a news feed so as to be kept informed about fraudulent products.

#### 4.2.4 Japan

After an unsuccessful research on the Japanese Law Translation webpage (66), which is accessible from the Japanese Ministry of Health, Labour and Welfare website (67), no Act or Law was found related to falsified pharmaceuticals to be summarised in this section. This however does not necessarily mean that the Japanese government has not promulgated a law on this matter; it might have not been translated yet.

The only law regarding pharmaceuticals that has been translated into English, which was published on August 10, 1960, and is entitled ‘Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices’, was promulgated with the purpose of improving *health and hygiene by providing the control required for securing the quality, efficacy and safety of pharmaceuticals*, amongst others (68). It was further modified in 1961 by the ‘Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices’ (69), and the ‘Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices’ (70).

#### 4.2.5 Other countries

The ‘Operation Volcano – The Herceptin Case’, whose story was published and is accessible online from (71), and that can be quickly summarised as the subtraction and manipulation of a hospital-use only drug in order to introduce it in other European countries (72), set the precedents for AIFA 671/2015, the Italian Medicines Agency (AIFA, from its acronym in Italian, *Agenzia Italiana del Farmaco*) law that legislated the former transalpine national Task Force, which had been however proposed on article 142 ter of *Decreto Legislativo 219/2006*. Nevertheless, this law was left behind after the promulgation of *Decreto Legislativo 17 marzo 2014*, which ratified European Directive 2011/62/EU (73).

Argentina has been a pioneering country in the field (**Figure 9a-d**), holding a total of five national-wide legislative actions since the first one promulgated on November 26, 1997. All of them are accessible from the Medicines Traceability System, run by the Medicines, Food and Medical Technology National Administration (ANMAT from its acronym in Spanish, *Administración Nacional de Medicamentos, Alimentos y Tecnología Médica*) (74). Thus, even though since 1997 the Argentinian government has established a controlled path for industry to provide the nation with genuine products, the first ever law that targeted individual units rather than batches, named *Resolución Ministerial N° 435/2011*, set the precedents for the development and the beginning of legislation of the matter. In accordance with the recommendation made by the WHO, that suggested all countries to create a legal framework that embraced the whole process of bringing pharmaceuticals to patients, the Latin American government promulgated the 10-articles-wide law that obliged natural persons or legal entities to implement a traceability system from production to importation (75).

Another Latin American country worthy of mention regarding pharmaceuticals serialization is Brazil. Accessible from the *Medicamentos* (medicines in Portuguese) directory at the National Sanitary Vigilance Agency (ANVISA from its acronym in Portuguese *Agência Nacional de Vigilância Sanitária*) webpage, one can grab access to a summary list of all the legislative texts that are currently into force in the country in regards with medicines. Thus, it is on part 4.3 where the National Medicines Tracking System (SNCM from its Portuguese acronym, *Sistema Nacional de Controle de Medicamentos*) is mentioned, being the first listed law LEI 11903/2009 *Rastreamento da produção e do consumo de medicamentos por meio de tecnologia de captura, armazenamento e transmissão electrónica de dados*, which has been modified afterwards by other legislative texts that are also linked on below (76). Especially relevant for this MSc's dissertation is the RDC 157/2017 (77), which regulates the implementation of the tracking system. VII Chapters and 21 Articles legislate the transition of 'experimental' to 'fully-operating', being remarkable the following three definitions from Art. 3°:



**Figure 9. Argentinian Pharmaceuticals Traceability System.** (a) Specific recommendations are given for each legitimate supply chain node; (b) patients can access an online portal to check the traceability of acquired medicines; (c) the link takes the internet-user to a PDF file that lists the APIs to be traced, as well as the pharmaceutical formulation; (d) access to a short guide is provided on how the system works. Screenshots acquired from <http://anmat.servicios.pami.org.ar/> on March 09, 2019.

a) *II. Código serial: código individual, contido no IUM, único por apresentação, composto de 1 a 20 caracteres alfanuméricos.*

Serial code: individual code contained in the UMI, specific to each presentation, and which is made up of 1 to 20 alphanumeric characters.

b) *IX. Identificador Único de Medicamento – IUM: uma série de caracteres numéricos, alfanuméricos, ou especiais, criada através de padrões de identificação e codificação, que permita a identificação individualizada, exclusiva e inequívoca de cada embalagem comercial do medicamento.*

Unique Medicine Identifier –UMI: a numeric, alphanumeric, or special characters series, created by identifying and codifying patterns that allow individual, exclusive and unambiguous identification of each commercial unit.

- c) *XIII. Número Global de Item Comercial (GTIN, sigla em inglês de ‘Global Trade Item Number’): identificador-padrão de artigo comercial, internacionalmente reconhecido, com quatorze dígitos.*

Global Trade Item Number (GTIN): commercial 14-digits identification pattern, internationally recognized.

On Art. 5º, the data that should be contained on the UMI is listed, being it a) GTIN presence, b) ANVISA medicinal presentation registration number, c) serial code, d) expiry date, and e) fabrication batch. Besides, on Art. 9º it is stated that *as embalagens comerciais dos medicamentos incluídos no escopo do SNCM devem conter o DataMatrix e a inscrição do código serial* (the medicinal commercial packages inscribed in the SNCM must contain a DataMatrix and a serial code), further emphasizing that *§ 1º o previsto no caput deve assegurar a leitura por mecanismos de captura eletrônica de dados e deve ser inscrito de forma legível ao olho humano* (the previously established must guarantee readability by electronic methods and must also be written in a human-readable manner).

#### **4.3 Technological strategies against drug counterfeiting**

The detection of shoddy pharmaceuticals is possible on the basis of impurity profiling, as products not manufactured under Good Manufacturing Practices (GMP) conditions have higher numbers than legitimately produced drugs (30). Nevertheless, the use of new technologies is usually restricted to higher-income countries due to unpredictable power breakdowns, extremely elevated temperatures and air humidity, and shortages in the supply of consumables or chemicals that occur in developing countries (25). Thus, even though it remains a challenge to develop a low cost, highly safe and convenient technology for tracking drugs (78), inexpensive devices such as Minilab® have been produced (26), so efforts must still be placed upon the development of these new technological strategies, which might be based on technical innovations and new initiatives (12), such as spectroscopy, X-ray methods, data matrix type, RFID labels, holograms, engraving, invisible prints, and nanotechnologies. All these new technological strategies may help increase the efficacy of detection of substandard/counterfeit pharmaceuticals (13) in field rather than within laboratory facilities, which significantly limits the width of the screening (9).

Raman spectroscopy, a non-invasive and non-destructive technique that allows counterfeit detection, presents itself as an interesting approach to counteract spurious pharmaceuticals. It preserves samples, should further analysis be warranted, although its

biggest drawback is the fact that it cannot include every possible drug product in the spectral library, including the different spectra produced by different legitimate finished products on account of different coatings and inactive ingredients (27). Alike Raman spectroscopy, hyperspectral imaging is a non-destructive technique that allows for the examination of dozens of samples at the same time through the support of mathematical and image analysis and processing methods that enable to distinguish, with nearly 100% probability, between the original and the counterfeiter (2).

Directional reflectance (DR) was proposed by Wilczyński, S *et al.* in 2016 as a new, rapid, reproducible, reliable and cheap method for distinguishing original drugs from counterfeiters outside of a laboratory environment. DR can be carried out in by the police, border guards and other services without any training given the portability and easy-usefulness of the reflectometer, which only requires applying its aperture to the tablet surface and pressing the trigger to provide qualitative and quantitative differences of the surface structure. Its biggest limitation is its applicability only to solid dosage forms, although minor modifications would allow the analysis of other forms (9).

Nevertheless, out of all the new potentially useful strategies to counteract spurious pharmaceuticals mentioned above, Radio Frequency Identification holds a predominant position. It is a wireless use of electromagnetic fields (78) that uses information stored and remotely retrieved on transponders to provide automatic identification (19) of tags attached to objects, animals or persons; which makes it highly efficient at tracking and tracing (79). It was first described to be useful for the drug supply chain during the establishment of the latter in 1996, although it was not reported to be used until 2005, when Pfizer used it to tag bottled medicines. Notwithstanding, during a pilot project orchestrated by the FDA, problems were found, such as the fact that unmatched frequency could cause interference and insufficiency of the readable distance (78). Moreover, its high implementation costs, over \$25 for active tags, and 7-15 cents for passive tags, and its rewrite-ability, that threatens the safety of stored information, may present a significant barrier to RFID adoption (15).

The DataMatrix or 2D codes is as predominant against counterfeiters as RFID on account of its high-capacity and error-correctability; and also because it has comprehensive reading and fast generational abilities. Thus, whereas a traditional bar code only enables to carry 12 to 20 characters, which is inadequate for drug security, 2D codes (78) are designed to hold information for a) Manufacturer Product Code (GTIN) –14 digits-, b) Expiry Date -6

digits (YYMMDD)-, c) Batch/lot Number –up to 20 alpha-numeric characters-, and d) Unique Serial Number –up to 20 randomized alpha-numeric characters (80). DataMatrix codes have been tested *in situ* in Sweden and Turkey. In the Scandinavian country the test was run for a pilot project to analyse the reliability and user friendliness of the codes. The results elucidated that although illicit products were identified before being dispensed to the patient, their entry into the legitimate supply chain could not be averted. The same holds true for Turkey, although Fadlallah, R *et al.* state that no empirical data was provided to support this claim. Besides, due to its quickness in detecting shoddy drugs, DataMatrix ensures high accuracy and security at a relatively lower price compared to RFID tags (6).

#### **4.4 Pharmaceutical logistics**

The legitimate supply chain (LSC) can be defined as *any supply chain that is either regulated/licensed by a ministry of health or other regulatory body or any supply chain where a patient would reasonably expect to obtain authentic products, supplied via a controlled supply chain, from the manufacturer of the product to the point of dispensing*. Penetration of counterfeit medicines into the LSC however has been reported for both weak and highly controlled chains alike, such as counterfeit antimalarials being detected in community pharmacies and counterfeit anticancer drugs being detected in the US (81).

The biggest attractive targets for counterfeiters are drugs that are often used in emergency situations, such as outbreaks or pandemics, where the supply of bona fide products may be limited (82). In such situations, the whole LSC is at risk, from contribution to storage, transportation and distribution, entailing the secondary wholesalers the critical point, as they do not deal directly with drug manufacturers, but rather buy and sell drugs in response to market shortages and surpluses (19). This clearly indicates the need for further research to address existing vulnerabilities and LSC complexities that are contributing factors for counterfeit penetration (81).

##### 4.4.1 Security within the supply chain

In some regions of the world, the trafficking of counterfeit medicines are crimes of opportunism, and in others, a part of a complex and organized global criminal enterprise (81). Regardless, onsite quality inspections at different levels of the LSC could offer an efficient and cost-effective intervention for preliminary testing; specially in countries that lack adequate national laboratories, as only the suspicious samples are sent for further testing (6).

As of February 8, 2019, the Friday before the entry into force of Directive 2011/62/EU, the AEMPS published on its website a short Informative Note to remind the change in the pharmaceutical industry legal framework. The Note emphasized that four years since the publication of the ‘Strategy against falsified pharmaceuticals’, no rogue pharmaceutical had been found within the legal channel, as opposed to what had happened in other European countries. Moreover, the steps taken by the Spanish government to ensure a secure LSC are detailed, as well as the characteristics of the ACM to be adopted from February 9, 2019, onwards. Thus, a unique identifier and an anti-tampering device should be placed on the outside package of all prescription drugs (and in no-prescription drugs if estimated necessary), unless otherwise stated due to low risk. That way, just before being used, the medicine could be verified to be authentic: the anti-tampering device must not be manipulated, and the unique identifier must coincide with the data registered on the repositories system (83).

As indicated on ‘Commission Delegated Regulation (EU) 2016/161’, the repository systems, in accordance with Article 35(1)

- (a) *shall be physically located in the Union;*
- (b) *shall be set up and managed by a non-profit legal entity [...];*
- (c) *shall be fully interoperable with the other repositories composing the repositories system [...];*
- (d) *shall allow the reliable electronic identification and authentication of individual packs of medicinal products [...];*
- (g) *shall maintain a complete record (‘audit trail’) of all operations concerning a unique identifier [...] (58).*

Thus, the repository system is managed in Spain by the Medicines Verification Spanish System or SEVeM from its Spanish acronym (*Sistema Español de Verificación de Medicamentos*), a non-profit legal organization dependent on the Ministry of Health, Consumption and Welfare. The repository will be connected to its fellow European homologous to allow a force of 140 000 agents to safeguard the market (84).

To make sure all countries within Europe apply the same terms to provide individual packages with a unique identifier, defined on Article 3(2)(a) as *the safety feature enabling the verification of the authenticity and the identification of an individual pack of a medicinal product*, the European Commission felt obliged to write up which are the technical



specifications the aforementioned unique identifier must be composed of; which are gathered on Article 4(a) to (e):

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

Article 5(1) *Manufacturers shall encode the unique identifier in a two-dimensional barcode*, Article 5(2) *the barcode shall be a machine-readable Data Matrix*. Moreover, it is also stated that whenever possible due to package dimensions, Article 7(1) *manufacturers shall print the following data elements of the unique identifier on the packaging in human-readable format:*

- (a) the product code;*

*(b) the serial number;*

*(c) the national reimbursement number or other national identifying the medicinal product, if required by the Member State where the product is intended to be placed on the market and not printed elsewhere on the packaging (58).*

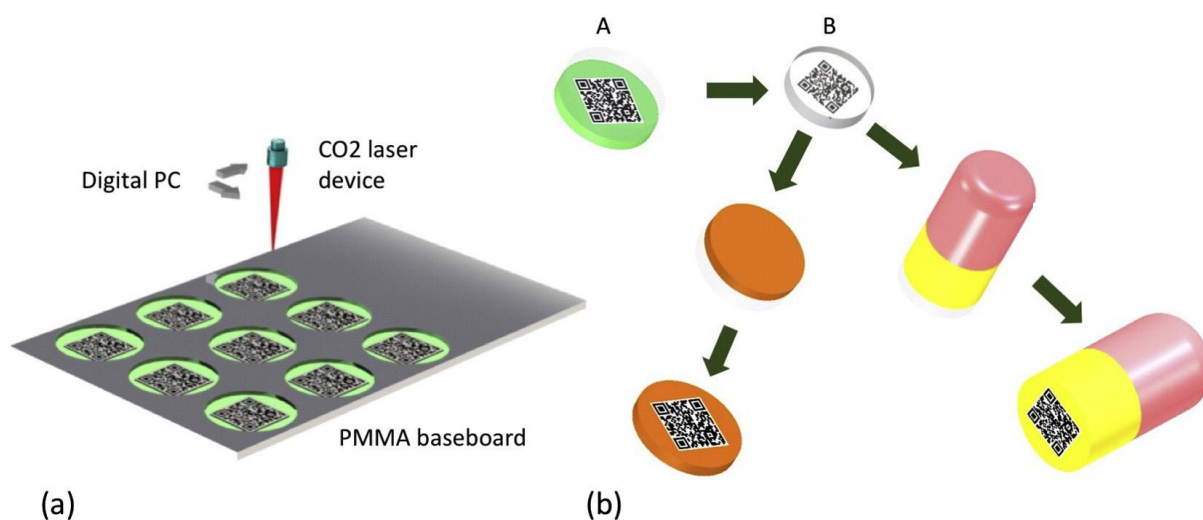
## **5 Discussion**

The Pharmaceutical Security Institute indicated an increase of more than 10-fold within 2002-2012 in reports of fake drugs (85). The increase, although still worrying, is however the result of the cooperation between nations and entities within nations, which have dedicated more resources to counteract this everyday-growing worldwide problem. Thus, even though a lot still remains to be done, the goal of a world without shoddy pharmaceuticals could be met in the near future, should the legislation become tougher against unscrupulous criminals who want to make profit by gambling with someone else's health. For instance, it has even been estimated that if the goal is met by 2030, nearly 3 billion cases of malaria will be averted, and 10 million lives will be saved, turning the cost of \$5-8 per case averted into one of the most cost-effective investments in public health (12).

Lopez Hurtado, R and Carvalho Lasmar, M (31) examined the association between a public awareness campaign on the dangers of counterfeit medicines from illicit drug market and changes in the behaviour of consumers. In summary, it was found out that, of those who received messages about the dangers of the street medicine market, 60.9% changed their behaviours, against 22.2% for those who did not receive any message, making clear that awareness-raising campaigns have an effect on consumers decisions. However expensive these campaigns might be for ministries or governments, results prove that they would be cost-effective in short periods of time, as the biggest advantage for criminals is the lack of awareness of the consumers, who are often attracted by the cheap prices and the possibility of acquiring prescription drugs without visiting physicians, whether or not they might be embarrassed of their pathology. Making patients be leery about the authenticity of the products they are obtaining would not only benefit their personal well-being, but also society as a whole, as criminals will be left without a market, hospitals will not be overloaded with patients whose pathologies have worsened, or who have suffered an adverse reaction after recreational drug abuse, and more jobs will be created.

Serialization can have unintended benefits other than ensuring no counterfeit product entering the LSC, such as a) expedited recall facilitation, b) better supply chain visibility, and c) enhanced product tracking (86). Anyhow, given the extremely lucrative business that dealing with fake pharmaceuticals is, serialization shall not be enough, or at least to provide a global protection, regardless of how much investment is placed upon; yet the effort will still be worth it, as it will help spare so many lives.

Several (11)(13)(21)(26) are the authors that express their concerns about the lack of visibility of the counterfeiting of drugs within the biomedical publications. They claim that most cases are reported either in newspapers or online, which is either a consequence or the reason this dearth of methodologically rigorous studies to prevent drug counterfeiting exists. Consequently, scientists should also turn an eye on this problem to help policy-makers take action according to where the problem truly lies within. Furthermore, the laboratory work could lead to the development of new strategies that, together with new policies, would help tracing any given formulation down to its origin solely on the pharmaceutical itself and not through its packaging (85). Albeit pharmaceutical packages and/or blister cards are printed with anti-counterfeiting codes, this might not stop criminals from replacing them, so it might be that in the future, techniques as the one presented on **Figure 10** may become a reality (78).



**Figure 10. Jie Fei and Ran Liu's proposal of drug-laden 3D biodegradable label using QR codes.** (a) Diagram of engraving QR codes over polymethyl methacrylate (PMMA), chosen as mould plastic on account of its transparency, easy processing, light weight and insulative, aging and corrosive resistances, among others; (b) Replication of the PMMA sheets to biocompatible materials. Figure obtained from Fei, J and Liu, R (2016).

## **6 Conclusions**

Given the current scenario where shoddy pharmaceuticals are easily available to patients, the need for governments to provide citizens with genuine medicines is being put at a halt. Thus, besides enforcing their legislations, which all countries should agree on, otherwise criminals might still find their ways to illegally operate; governments should set aside monetary resources in order to bring about one of the most powerful strategies against counterfeiting: knowledge.

It has been widely proved that awareness-raising campaigns do have an effect on protecting people's health, so they should be more widely advertised, both in developed and developing countries, given that they are as likely to suffer from such criminal acts, either because patients want to hide their conditions, because of drug abuse, because it is a way of saving money (or so they think), or because it is the only way to get hold of medicines. Anyhow, regardless of the way or the why of the acquisition, making patients be leery of what they are acquiring will destabilize the circle, consequently protecting them.

Despite the almost perfect execution of pharmaceuticals manufacturing by criminals, they can still be tracked and traced. Nevertheless, the problem nowadays is that the countries where the applied techniques for that track-and-tracing are the most needed, are also the countries that cannot afford for the infrastructure to hold the laboratories. Thus, one of the biggest challenges worldwide is to be able to provide developing countries with these resources within their borders. Furthermore, it would be highly beneficial to also develop techniques or gadgets for the purpose that can be manipulated by non-educated people, hence only submitting for farther analysis those samples indicated as adulterated.

Hence, what can be drawn from this study is that the problem is known, and measures are being taken so as to mend the situation, albeit cooperation between countries is a must, whether through treaties or any other international agreement. Besides, more visibility on biomedical publications should be dragged to the matter, as that could help develop new strategies to detect counterfeiters before it is too late.

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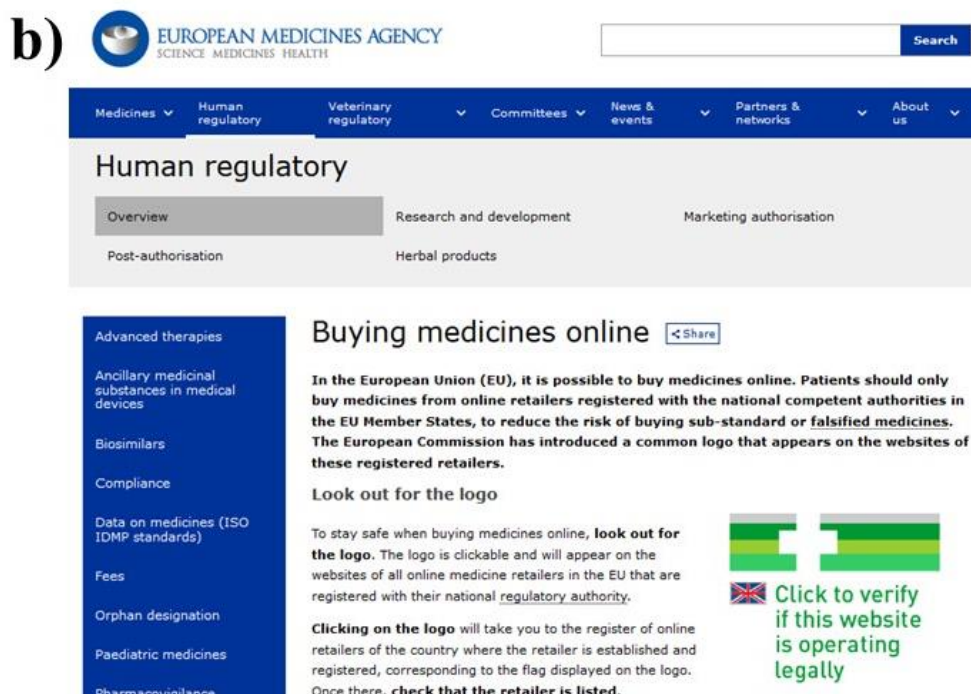
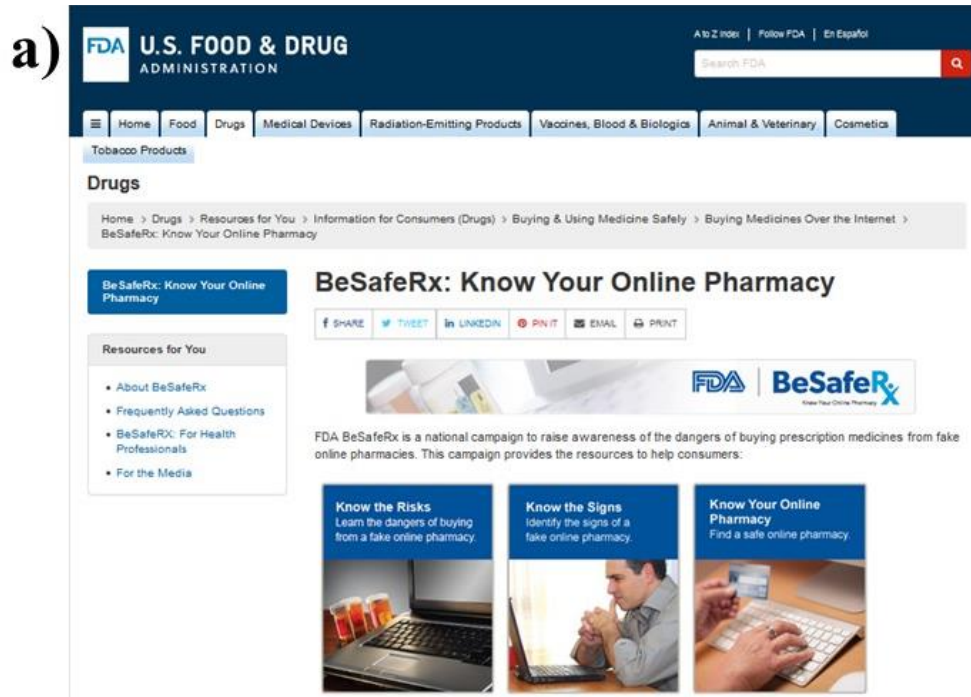


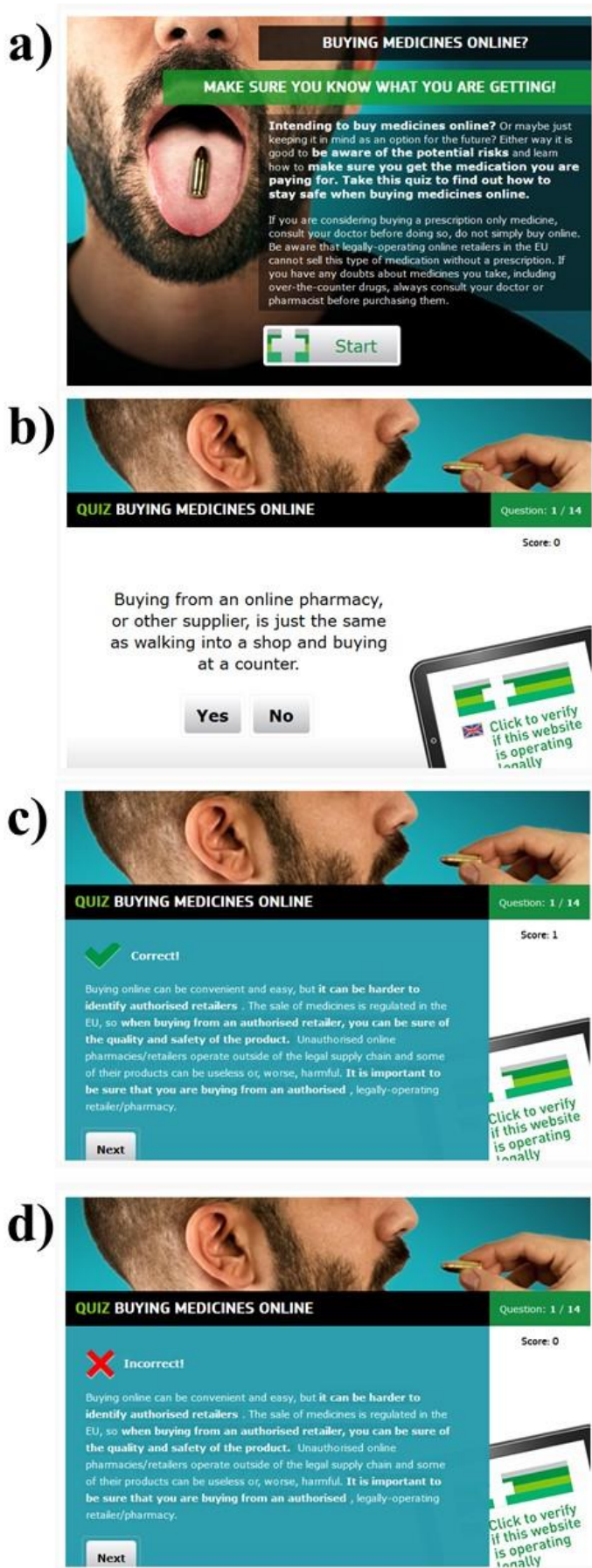
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**Annex 1. FDA and EMA websites screenshots.** (a) ‘The BeSafeRx: Know Your Online Pharmacy’ site provides information in plain English about the risks and the signs of fake online pharmacies, as well as access to an interactive USA map from where one can check which are the legitimate online pharmacies operating in each State; (b) the EMA warns European citizens to look out for the clickable logo, which will take the Internet-user to the register of online retailers of the country where the retailer is established and registered. Screenshots acquired from www.fda.gov and www.ema.europa.eu, respectively, on January 22, 2019.





**Annex 2. EMA ‘Buying medicines online?’ quiz.**

Besides challenging one’s knowledge, this interactive quiz is featured in such a way that the European logo is always on display, so as to make sure the Internet user gets familiar with it. (a) Internet-users can take this interactive quiz developed by the EMA to learn about the risks of buying pharmaceuticals online, and which are the best ways to keep one’s self safe; (b) up to 14 yes-or-no questions trick the Internet-user’s knowledge; (c) points are awarded every time a question is correctly answered, besides providing the reasons why that is true; (d) incorrectly answered questions do not deduce any point, but instead teach the Internet-user why their answer was wrong. Screenshots acquired from <http://ec.europa.eu> on February 15, 2019.

**Annex 3. Signatures and ratifications of the Medicrime Convention.** Information extracted from website, www.coe.int, on May 1, 2019.

<i>MEMBERS OF THE COUNCIL OF EUROPE</i>			
<i>Country</i>	<i>Signature</i>	<i>Ratification</i>	<i>Entry into force</i>
<b>Albania</b>	17/12/2015	06/06/2016	01/10/2016
<b>Armenia</b>	20/09/2012	05/02/2016	01/06/2016
<b>Austria</b>	28/10/2011		
<b>Belgium</b>	24/04/2012	01/08/2016	01/11/2016
<b>Bosnia and Herzegovina</b>	04/12/2015		
<b>Croatia</b>	03/09/2015		
<b>Cyprus</b>	28/10/2011		
<b>Denmark</b>	12/01/2012		
<b>Finland</b>	28/10/2011		
<b>France</b>	28/10/2011	21/09/2016	01/01/2017
<b>Germany</b>	28/10/2011		
<b>Hungary</b>	26/09/2013	09/01/2014	01/01/2016
<b>Iceland</b>	25/10/2011		
<b>Italy</b>	28/10/2011		
<b>Liechtenstein</b>	04/11/2011		
<b>Luxembourg</b>	22/12/2011		
<b>Portugal</b>	28/10/2011	18/12/2018	01/04/2019
<b>Republic of Moldova</b>	20/09/2012	14/08/2014	01/01/2016
<b>Russian Federation</b>	28/10/2011	20/03/2018	01/07/2018
<b>Slovenia</b>	06/03/2019		
<b>Spain</b>	08/10/2012	05/08/2013	01/01/2016
<b>Switzerland</b>	28/10/2011	25/10/2018	01/02/2019
<b>Turkey</b>	29/06/2012	21/09/2017	01/01/2018
<b>Ukraine</b>	28/10/2011	20/08/2012	01/01/2016
<i>NON-MEMBERS OF THE COUNCIL OF EUROPE</i>			
<i>Country</i>	<i>Signature</i>	<i>Ratification</i>	<i>Entry into force</i>
<b>Benin</b>	29/05/2018	29/05/2018	01/09/2018
<b>Burkina Faso</b>	16/02/2017	27/07/2017	01/11/2017
<b>Guinea</b>	10/10/2012	24/09/2015	01/01/2016
<b>Israel</b>	28/10/2011		
<b>Morocco</b>	13/12/2012		



**Annex 4. Citizen’s awareness-raising campaigns disclosed in Spain.** (a) AEMPS and UNODC campaigns emblems; (b-d) AEMPS ‘Do not buy counterfeit medicines over the internet. It can be lethal for your health’ campaign YouTube video frames. Screenshots acquired from <https://www.aemps.gob.es> on February 14, 2019.

**a)** Campañas informativas

Las estrategias frente a medicamentos falsificados tienen entre sus objetivos fundamentales concienciar a los consumidores sobre los riesgos asociados al consumo de medicamentos falsificados e ilegales, así como los dispensados ilegalmente al público. Para conseguirlo las autoridades sanitarias realizan campañas informativas dirigidas a la población general. La concienciación ciudadana ha demostrado ser en este sentido una de las actuaciones más eficaces para proteger la salud de la población.

Campaña “No compres medicamentos en webs ilegales.  
Es un error fatal para tu salud”

Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)



Campaña “Productos falsificados:  
no apoyes el crimen organizado”

United Nations Office on Drugs and Crime (UNODC)



**b)**



**c)**



**d)**

