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REVIEW

Pharmaceutical Serialization, a Global Effort to Combat Counterfeit Medicines

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Objective: Pharmaceutical serialization is a process in the pharmaceutical industry that offers a secure solution to track and authenticate drugs in the distribution chain. The unique recognition number for every drug unit helps to identify and combat counterfeit products. This paper aims to highlight the advantages of serialization implementation as an innovative tool to combat globally the counterfeiting drugs phenomenon. **Methods**: Worldwide a considerable effort was focused on enhancing medicines identification. Analytical methods, development of the new lab equipment, digital solutions, and blockchain technology are the new directions for the future. Also, legislation needs to be correlated at the international level between the pharmaceutical industry, distribution, and pharmacies. **Results**: A good collaboration between responsible entities should be implemented to protect public health and to promote patients' access to safe medicines. A directive implemented on European Union focused on fake drugs, Global Monitoring and Surveillance System launched by the World Health Organization, or the international campaign "Fight the Fakes" are remarkable examples. **Conclusions**: An efficient joint effort between the pharmaceutical industry and law enforcement is required. Counterfeit medicines are a worldwide threat to public health and demand a unitary pharmaceutical serialization system to be implemented as an ideal solution.

Keywords: serialization, counterfeit medicines, fake medicines, quality assurance, pharmaceutical industry

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Introduction

One of the essential requirements for a drug is the assurance of its quality, together with its efficacy and safety. In the pharmaceutical industry, professionals try to develop and improve analytical methods to assure prescribed treatment will improve patient life quality. On the other side, the patients have to trust in pharmaceutical companies integrity and acknowledge their concern regarding drugs safety. To achieve this ideal, quality of medicine, it is the most challenging mission in the drug development field [1, 2].

A collective joint effort between authorities from all over the world was made to ensure the patient's safety in the 21 century. World Health Organization (WHO), Food and Drug Administration (FDA), European Union (EU) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) gathered in their guidelines a common purpose. The goal is to help future research projects to find what was their background when they assure the quality of drugs and what can be used for developing new methodological decisions in upgrading the pharmaceutical industry. Every country applies general practices for drug assurance quality based on the submitted regulations. Essentially, there is a national compendium of good manufacturing practices (GMP) with specific chapters and annexes that maintain regulatory obligations [3].

Other emergent general practices in the field of the pharmaceutical industry are total quality management (TQM), quality risk management (QRM), quality by design (QbD), the application of corrective and preventive actions, process capability analysis, six sigma methodology, process analytical technologies (PAT), lean manufacturing, ISO series and the hazard analysis and critical control point methodology (HACCP) [3].

One of the recent requirement to improve drugs quality is their traceability. Drug serialization is a practice that assures a unique recognition number for every drug unit. The given number may be used for product tracking and authentication in the distribution chain, allowing counterfeits identification. It requires support and collaboration from all partners involved in medicine's marketing. There are several essential elements to be introduced in a serial number: a product code capable of giving essential characteristics like name, pharmaceutical form, concentration, package, batch number, expiration date, and a serial number obtained by a computerized algorithm. This serial number has to be unique and can not be repeated for at least five years since its introduction on the market (Figure 1) [4, 5].

The secured drug is checked in open circuit or hospital pharmacies by reading the bar code and receives from an integrated computer system the confirmation of its authenticity, thus being able to decommission it and assuring its safety to the patient. If the process reveals a non-com-

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pliance, the computer system issues an alert, and the drug is withdrawn being subsequently checked. The patient receives another medicine, verified to be authentic and has a total guarantee that the medication is genuine, the risk of being falsified approaching zero. The mechanism for serialization and verification of medicinal products is applied only to prescription medicines and is not required for over-the-counter medicines (so-called OTCs), dietary supplements and medical devices. Annually, almost 30 billion US dollars, represents worldwide counterfeit drugs, an illegal business, especially in low and middle-income countries [6].

Technologies have a significant impact in combating counterfeiting drugs process. Nowadays, it is straightforward to manufacture a product which may pass at first glance as an original. Also, the online drugs market (known as a *grey market*) is very accessible. Accelerated growth of the online pharmacies number could put people's lives in danger. Consequently, serialization process becomes a universal tool as a primary procedure in combatting counterfeiting [7, 8].

Pharmaceutical serialization emerged as a challenge to improve the traceability of drugs. It became an urgent necessity in a global effort to combat selling counterfeit medicines, a growing and dangerous phenomenon for patients' health. The general objective of this paper is to review the current general aspects of the implementation of serialization process. The specific goals are to outline the emerged modern methods to improve the serialization, the existing legislative regulation and the steps forward to global harmonization and the active mechanisms of serialization against counterfeiting medicines. Health care professionals are primarily targeted, along with specialists in the pharmaceutical industry. However, there is a lot of new ground in the area of supply chain management and serialization/traceability.

Counterfeit (or fake) medicines and identification methods

Counterfeit medicines are medicines which do not respect intellectual property rights and/or violate trademark laws. Counterfeiting can be related to product mislabeling to reproduce an authentic medicine. Another more dangerous method is to supply drugs without or with a lower/higher amount of active pharmaceutical ingredients (API). Also, a serious situation is when medicines contain non-labelled harmful toxic substances.

Fake drugs, as their name tells us, are those counterfeit drugs that are designed to mimic original medicines. Vital drugs such as those for the treatment of malaria, tuberculosis, HIV/AIDS and even anticancer drugs have not escaped forgery [9, 10].

Using a drug in a specific pharmaceutical form without required quality can cause severe side effects, possibly even death (Figure 2). To verify the authenticity of medicines at the personal level, "the six P's " were introduced: place, prescription, promises, price, privacy, and product are essential when a patient purchases a treatment [9, 11].

The most common counterfeit drugs

Recently, published data revealed a variety of percentages of falsified drugs based on the geographic areas: 10.5% of medicines are falsified or underdosed, according to WHO worldwide, about 10-30% according to CDC in developing countries versus almost 1% in the U.S. or 13% in Europe industrialized countries. The magnitude of this problem makes it harder to achieve universal access to safe and effective global medicines and the need for further investigation of well-designed prevalence studies are required to reflect the actual prevalence [10, 12-15].

The „lifestyle drugs" for weight loss and phosphodiesterase type 5 inhibitors (e.g. sildenafil or homologues) used for erectile dysfunction are the most prone to falsification in the countries with developed economies. Both categories can become a potential threat for health because they are targeting people who do not share their problem with healthcare professionals and prefer to buy anonymously, through the underground market [16, 17]. Several reported cases highlighted this dangerous phenomenon (Table I). The FDA has a rigorous legislative system regarding drug authorization. Still, there were multiple incidents reported publicly in the last years on their website (Table II).

Identification methods of counterfeit/fake medicines

Nowadays, analytical chemistry development in the pharmaceutical industry became an essential tool in counterfeit drug detection. Analytical techniques as HPLC or X-ray fluorescence are suitable for detecting the presence of illicit compounds because of high precision, high sensitivity detection, and short-time analysis [16, 17]. Unfortunately, it is difficult for the authorities to keep up with all pharmaceutical forgeries [1, 2].

The techniques used for verifying quality purposes have to overcome all the new attempts of falsification. At a visual

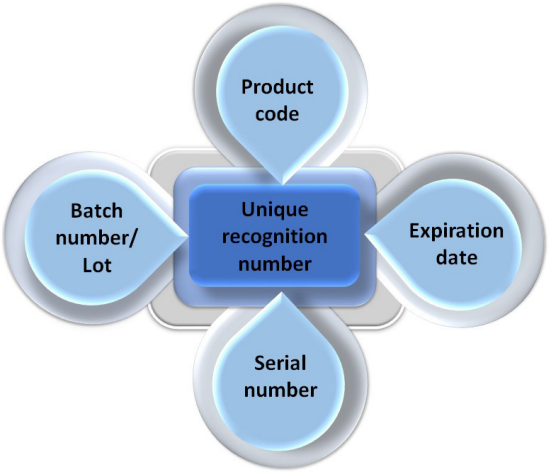

Fig. 1. Underlying elements of the unique recognition number of a drug unit in the serialization process.

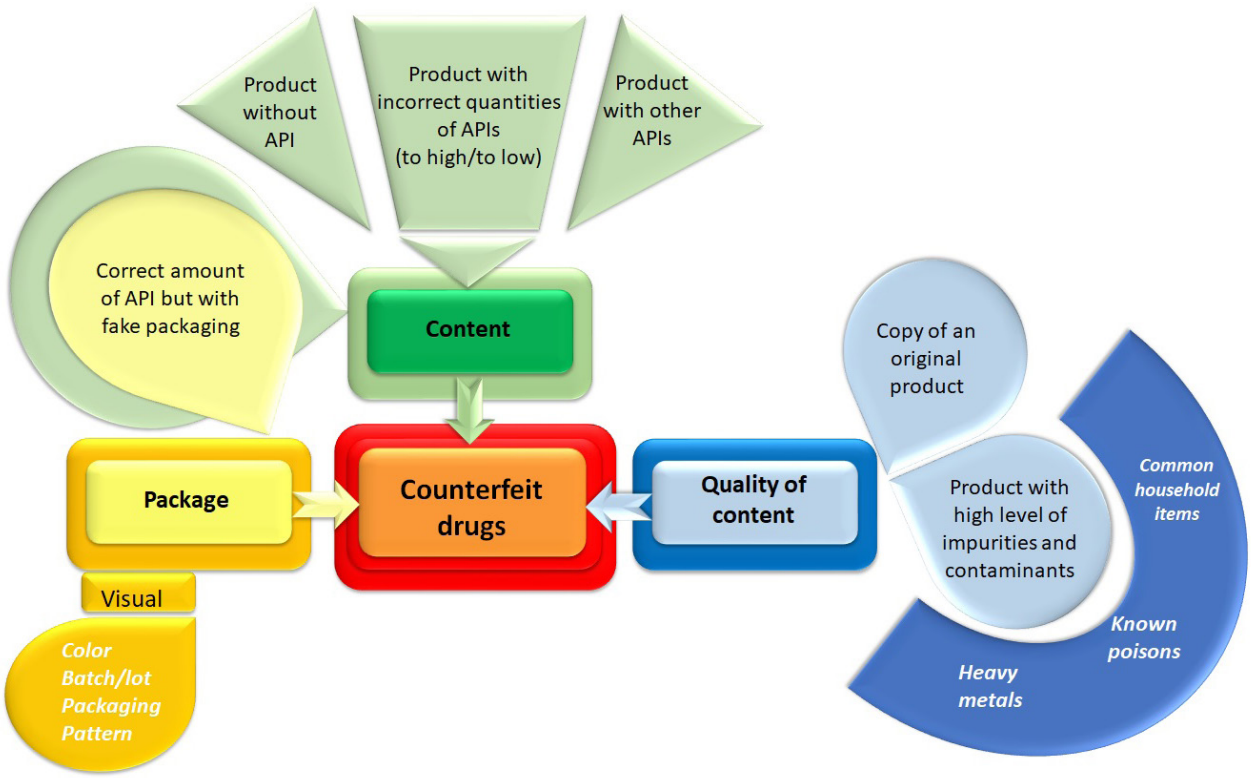

Fig. 2. The most common ways to falsify drugs.

Table I. Examples of counterfeit drugs identified in different regions of the world.

No.	Active pharmaceutical ingredient (API)	Counterfeit identification	Country (or region)	Ref.
1	Artesunate	Paracetamol	Asia	[46]
2	Isoniazid, Rifampicin	A low dose of the API	Estonia, Columbia, Russia, Vietnam, India, Latvia, Nigeria	[47- 48]
3	Amoxicillin Ampicillin Ketoconazole Metronidazole	Failure of quality tests	Nigeria	[48]
4	Rifampicin	Clonazepam	Canada	[49]
5	Amlodipine	Minocycline	Canada	[50]
6	Zopiclone	Furosemide	France	[51]
7	Bevacizumab	A mix of corn starch, salt, and other solvents	USA	[52]
8	Antimalarials	35% failed chemical analysis 20% were falsified leading to more than 100.000 deaths per year	Asia, Africa	[53]
9	Isosorbide-5-mononitrate	Pyrimethamine	Pakistan	[54]
10	Steroids syringes of methylprednisolone acetate	Deaths of fungal meningitis due to fungal contamination with Exserohilum rostratum	USAe	[55]
11	Antihypertensives, Isotretinoin	APIs have been degraded following storage or tests under accelerated stress condition	Several different countries	[56-58]

Table II. FDA case reports of market withdrawal [59].

No.	Active ingredient	Counterfeit identification
1	Lamotrigine tablets	Cross-contamination with enalapril maleate
2	Dietary supplements „Silver Bullet" (male sexual enhancement capsules)	Sildenafil - undeclared API, found in the product
3	Dietary supplements „Rhino" (male sexual enhancement capsules)	Sildenafil and tadalafil - undeclared APIs, found in the product
4	Dietary supplements „7K and Poseidon" (male sexual enhancement capsules)	Sildenafil and tadalafil - undeclared APIs, found in the product
5	Hydrocortisone (lots of „Piyanping Anti-Itch Lotion")	Dexamethasone
6	One lot of „Brilinta" (active ingredient: ticagrelor)	Lesinurad
7	Cyclobenzaprine HCl tablets	Amantadine HCl capsules
8	Apixaban („Eliquis") 5 mg	Apixaban („Eliquis") 2.5 mg
9	Pravastatin	Bupropion

level, both *„the real"* and *„the fake"* drugs are identical. *„The fake"* drug can even pass the conventional methods of identification. Thereby, these products do not treat pathologies because most of them do not contain any API. Sometimes,

in the composition of a fake the percentage of API is improper (overdosed or underdosed). Also, a counterfeit drug could contain toxic ingredients and could be produced and transported from one country to another without quality control [1, 18].

Scientists are making a considerable effort to improve their methods of medicines identification to combat this phenomenon. Their primary objective will be to develop or to transform lab equipment into portable, quick, efficient, and economical devices. Adaptation of multiple analysis technologies offers immediate results if there are additional facilities, the expertise level of operating agents and the costs of this transformation. These adapted analysis techniques were addressed to counterfeit detection, organoleptic inspection, identification, quantification of APIs, and confirmation tests (Table III) [19].

Forgery can be encountered both at original and generic drugs products. Thus, the challenge of the public health system depends on how adequate the used technologies are and, on their ability to be one step ahead of the counterfeiter [18, 20]. It is crucial to know the ways of obtaining illicit drugs to fight against criminals who produce counterfeit drugs (Figure 2). All of these opportunities can be diminished by innovative techniques and devices like multiple encrypted databases [21, 22].

Counterfeit medicines can also be identified based on reports from the national pharmacovigilance (PV) system. It is mandatory to have a PV system in every country, where a basic reporting system can establish adequate communication between public health institutions and legal authorities. The World Health Professionals Alliance was actively involved in raise awareness of counterfeiting drugs for all healthcare professionals. Combating this dangerous phenomenon requires good interdepartmental cooperation, harmonized legislation and the application of criminal justice [2].

New directions to improve drug quality and security by serialization

Pharmaceutical industry field and legislation are evolving rapidly around the world. Governments demand traceability to ensure all steps in the distribution chain can be backtraced, from production to pharmacy and patient. The detailed model assures an electronic pedigree for every produced single unit medicine and helps to trace all distribution chain from the manufacturer to the patient, knowing the history and the transactions [22, 24]. New digital solutions to combat false drugs can be used: radio frequency identification, advanced computational methods, online verification, blockchain technology [5, 22, 25]. For example, the implementation of a Decentralized Application (DAPP) has been coded and tested as a prototype on the Ethereum Ropsten blockchain network [5].

Radiofrequency identification is a modern way of tracking the drug. Entities responsible for regulatory safety recommend various authentication measures like holograms, invisible printing, and a global trade item number. Anticounterfeiting directives can be more efficient if combine at least two of the methods above [21, 26].

Serialization is a millennial process that refers to track and trace drug units. This process is obtained by adding an electronic pedigree and a unique identification number to the original individual package. The main goal of pharmaceuticals serialization is to have an individual and exclusive identifier related to each unit of medicines [8]. An international mobilization and public security and policy will help both the authorities and population to be protected from counterfeits medicines. The 2D barcodes to vaccines, medical devices or drugs can help the responsible organizations by promoting an efficient inventory process, also, essential data in ways of worldwide distribution [18, 27, 28].

Other emergent objectives of pharmaceuticals serialization are:

- to stop undermining people's trust in the health system and pharmaceutical manufacturers;
- to not waste money on ineffective therapies because of an insufficient amount of API or even the complete lack of API;
- the urgent need for global collaboration between pharma industry and law enforcement and implementation of harsher penalties for those who threaten human's life.

Serialization requires the collaboration of partners involved in the process of drug marketing [4, 17, 30]. Regulations on drug serialization are expected to cover about 70% of all existing drugs. Currently, there are no common international standards. Implementation, coordination, and control of serialization require substantial financial investment and a good understanding of rules [4, 30].

The consolidation and adoption of applicable regulations at the international level are expected. The priority of the ICH is the safety, efficacy and quality of medicines,

Table III. Technologies for detecting substandard medicines (Capillary electrophoresis = CE, Gas chromatography = GC, Thin Layer Chromatography = TLC, High-Performance Liquid chromatography = HPLC, Fourier-Transform Infrared Spectroscopy = FTIR, Near-Infrared Spectroscopy = NIR, Nuclear Magnetic Resonance Spectroscopy = NMR) [19].

Portable technologies		**Technologies that require a research lab**	
Technology	Purpose	Technology	Purpose
Colorimetry	Initial classification	CE	Chemical identification, separation, and quantification
Refractometry	Dissolving	GC	Chemical identification, separation, and quantification
TLC	Chemical identification, separation, and quantification	HPLC	Chemical identification, separation, and quantification
FTIR spectroscopy, NIR spectroscopy, Raman spectrometry	Chemical profiling	NMR Spectroscopy	Chemical profiling

criteria that underlie the authorization of drugs. Cooperation in the field of regulations ensured with the help of the International Forum of the regulatory authorities for efficient and rapid exchange information. International collaborations in the EU also involve WHO.

Drug serialization helps the pharmaceutical industry to deliver controlled and safe medicines. Nowadays, globalization affects drug serialization. In 10 years by now, the track-and-trace on item level will be required by law, as a globally standardized authentification method. The urgent need to keep on updating this process like using anti-counterfeiting material inks, or changing from authentification model to an electronic pedigree with a constant update of 2D barcode scanning is because of the existence of illegitimate online pharmacies or grey markets. Patients will be able to check on smartphone what they bought online and can retrieve information about a specific product by scanning the unique identifiers. Thus, it is established a direct trust relationship between manufacturer and patient [6, 8, 28].

There is another category of medical errors based on the List of Confused Drug Names (Look-Alike Sound-Alike, LASA) that can put patients in danger. There are many obstacles to overcome because of the phonetics and linguistic terms complexity between countries. The similarity between the phonetic-orthographic name of drugs can lead to numerous errors, for example, the confusing name between doxorubicin-daunorubicin-idarubicin, aripiprazole-albendazole or Adderall-Inderal. Healthcare organizations have been working on computer algorithms as prevention strategies to detect similarity between brand name or to increase background differences of the labelling. Regarding prescribing and dispensing procedures, it is an urgent need to have a common database and a standard regulation that can keep errors at a minimum level [31].

International regulation regarding pharmaceutical serialization

Counterfeiting of medicines is an international criminal phenomenon, translated into a threat to public health and damage to the manufacturer's image. Worldwide regulators are moving forward with the implementation of the track-and-trace serialization process [30]. Since 2013, the EU has a directive about counterfeit drugs and consequently became more accessible for the authorities to control their traceability. In the EU is an extensive network that sums up approximately 50 regulation authorities from 31 countries, the European Medicines Agency (EMA) and the European Commission (EC) [32].

The EU system works efficiently if the member states share the workload. The security of all drugs that are available on the EU market is monitored by the European system of drug regulation throughout their lifetime. The EMA has a committee dedicated to the safety of medicinal products for human use named Pharmacovigilance Risk Assessment Committee (PRAC) which intervenes in the case of a safety issue of a medicinal product and offers advice and recommendations to the authorities so that the risk-benefit ratio assessment is positive [33]. EU 2011/62 directive comprises in the authentication and identification of all drugs, except the ones on the Whitelist. Also, just to cope with these problems, the EU has an EU HUB, a central network storage from which the information is transferred to national networks [34].

Starting with 2013, in the US, is available the Drug Quality and Security Act (DQSA). DQSA clearly outlined the steps required to create a secure electronic system (Figure 3) that would reference the identification and traceability of specific drug prescriptions circulating on the US market. By 2023, DQSA is expected to improve as follows: electronic transactions for each prescription issued,

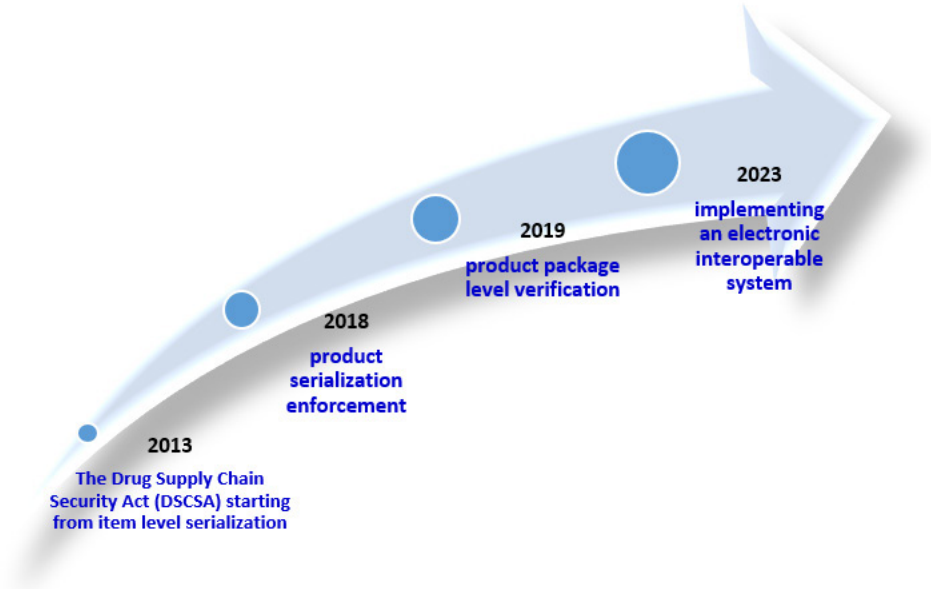

Fig. 3. Evolution of serialization from product item to a unique package.

verification of the specific identifiers of each product at the unique package level, a quick response regarding illegal and suspicious products, when found, improved efficiency of recall of medicines [27, 35, 36]. The FDA considers the guideline on drug serialization to be the first of several regulations that will be introduced in the future regarding the identification of drug products [37].

Facing numerous counterfeit cases and based on the partnership in the convention of European Council MEDICRIME, Russia took action. It added in their Criminal Code, three particular articles that refer to measures to identify and neutralize falsified drugs. Thus, it is mandatory to have a collaboration between law enforcement and pharmacy specialists to provide and apply effective criminal penalties [29, 38].

Starting with February 2019, it has become compulsory, with very few exceptions, for the manufacturers from Romania to mark the medicines under the prescription with the new safety elements based of the EU Directive 2011/62 [39]. The provisions of the Counterfeit Drugs Directive have been implemented in the national legislation. The provisions of the Delegated Regulation 2016/161 have been entered into force in the territory of Romania. The Organization for the Serialization of Medicines in Romania (OSMR) was established, a non-governmental, nonprofit, independent, autonomous, and apolitical organization for the implementation of the European Directive no. 2011/62/EU is referring to counterfeit medicines and Delegated Regulation 2016/161. Currently, OSMR is responsible for the National Medicines Check System (SNVM). SNMV is a part of the European Medicines Verification Organization (EMVO). Through EMVO platform, pharmacies and other entities from the health domain can verify the authenticity of a pharmaceutical product [40].

The International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use (ICH), founded in 1990, is responsible for the promotion of public health through technical guidelines implemented by regulatory authorities. ICH's priority is the safety, efficacy and quality of medicines, criteria that underlie the authorization of drugs [41]. An efficient and rapid exchange of information is assured through the International Forum of the regulatory authorities in the pharmaceutical sector [32]. Globally, a collaboration between every state authority regarding human medicine should be mandatory.

Perspectives in implementing serialization

In 2013, WHO launched the Global Monitoring and Surveillance System (GSMS) to encourage reporting the counterfeit drugs in a systematic and structured format, and to enable the creation of an international database of tracking and detection system [42].

Recently, WHO has issued drug alerts and numerous regional threats and has provided technical support in over 100 cases. WHO has trained over 550 persons to deal with the authorities' relations department in 141 Member States to report falsified medicinal products to the GSMS. WHO also works with eighteen of the largest public procurement agencies. The matrix code inserts the necessity of advance technology on every package. Going from one-dimensional linear code like Global Trade Identification Number to two-dimensional linear codes like 2D Data Matrix, the one utilized in pharmacies, means that overtime robustness is higher in the second case causing its identification even at 40% damage of the code [28, 34]. New technologies have increased their optimization process, including nanotechnologies or invisible prints, and holograms [14].

The mechanism of Member States is the global platform where countries can agree, coordinate, decide and organize actions against drug counterfeiting. Effective collaboration has been established between the Member States and the WHO. Unregulated websites, social media platforms and smartphone applications may be responsible for the sale of illegal drugs (Figure 4).

The Directive of 2011/62/EU introduced a mandatory logo, through Implementing Regulation 699/2014, addressed to online medicines distribution websites. The consumer is redirected to the list of authorized distributors to verify the authenticity of a site, only clicking on this logo [39, 43, 44]. Finally, society takes an attitude; an illustrative example is *"Fight the Fakes"* campaign that includes over thirty partners offering a thorough strategy for a significant impact on the population [45]. Strategic partnerships should be made to stop faking drugs and to providing the highest quality medicines.

Conclusions

The need to implement drug serialization comes as a consequence of multiple incidents of counterfeiting in the pharma field. Serialization is a valuable tool in combat-

Figure 4. Checking the authenticity of medicine by smartphone.

ing counterfeiting drugs. Technology development brings new methods to identify and ensure the safety of drugs as radio frequency identification, advanced computational methods, online verification, blockchain technology, nanotechnologies, invisible prints, and holograms. International regulations and legislation tend to harmonize, and more counterfeit drug surveillance systems are active and functional. New serialization mechanisms were created at the joint initiative of drug manufacturers, wholesale distributors and community pharmacists. Further attempts are being made to find new solutions to facilitate the serialization process, to update and speed up the identification methods of forgeries and to ensure a global collaboration.

Authors' contribution

GAP - Collecting bibliographic data; writing and preliminary revision of the manuscript
GH - Writing and critical revision of the manuscript; English correction
AR - Conception and design of the article; analysis and interpretation of collected data; final review of the manuscript.

Conflict of interest

None to declare.

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