Background

Since man began to brew potions, ointments and medicinal plasters to fight disease, adulterated products also appeared. Queen Hatshepsut of Egypt (circa 1500 BC) commissioned an expedition to search for genuine herbs, as the Egyptian markets were flooded with fake botanicals.\(^1\)

Around the 4th century BC, Theophrastus Eresos (circa 372 AC—286 BC), friend of Aristotle and follower of his philosophical works and the first great botanist known warned in his work of fake medicines of botanical origin.\(^2\)

Three centuries later, the Greek Pedanius Dioscorides (40 AC—90 AD), surgeon, pharmacologist and botanist, who accompanied the Roman armies as doctor wrote his famous work "De materia medica". Translated into at least 7 languages and used as pharmacology text for more than 15 centuries, these writings not only describe the medicinal value of plants, chemicals and natural products, but also point out the existence of a market of falsified medicinal products.\(^3,4\)

In England from the end of the 17th and during the 18th century, patent medicines grants were given by the kings.\(^5\) The name patent medicine is utterly misleading since there was no need to reveal their components or effectiveness; owners only paid to have a patented brand. Richard Stoughton's Elixir was one of the first compound medicines thus recognized. These early drug attempts constituted mixtures of water, with any part of plants (stems, leaves, roots, seeds, fruits and flowers), spices, alcohol (as a solvent and preservative) and sometimes sugar. Today some of these products are still used as flavoring for drinks or

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Counterfeit medicines, including the entire range of activities from manufacturing to providing them to patients, is a vile and serious criminal offence that puts human lives at risk and undermines the credibility of health systems. As a result of this meeting, the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) composed of 193 Member States of WHO was established on a voluntary basis and includes national and international organizations, agencies responsible for enforcing laws and regulations, drug regulatory authorities, customs and police organizations, non-governmental organizations, associations of pharmaceutical manufacturers and wholesalers, health professionals and patient groups, with the intention of making the national authorities and decision-makers in each country to establish effective legislative measures to combat drug counterfeiting.

"Poor quality medicines" is a term inclusive of counterfeit, substandard, and degraded medicines and also for medicines that fail chemistry analysis but with insufficient information to determine whether they are counterfeit, substandard, or degraded. The available data do not allow relative sizing of the area of...
each circle in proportion to the frequency of type of poor quality medicine. There could be grey areas between all three main types. For example, both substandard medicines and counterfeits could become degraded after manufacture.(15)

**Definition of Counterfeit Medicines**

IMPACT in its 2008 meeting, together with WHO, gave a very comprehensive definition of counterfeit medical products:(14)

The term counterfeit medical product describes a product with a false representation (a) of its identity (b) and/or source (c). This applies to the product, its container or other packaging or labeling information. Counterfeiting can apply to both branded and generic products. Counterfeits may include products with correct ingredients/components (d), with wrong ingredients/components, without active ingredients, with incorrect amounts of active ingredients, or with fake packaging.

Violations or disputes concerning patents must not be confused with counterfeiting of medical products. Medical products (whether generic or branded) that are not authorized for marketing in a given country, but authorized elsewhere are not considered counterfeit. Substandard batches of, or quality defects or non-compliance with Good Manufacturing Practices/Good Distribution Practices (GMP/GDP) in legitimate medical products must not be confused with counterfeiting.

Notes:
(a) Counterfeiting is done fraudulently and deliberately. The criminal intent and/or careless behavior shall be considered during the legal procedures for the purposes of sanctions imposed.
(b) This includes any misleading statement with respect to name, composition, strength, or other elements.
(c) This includes any misleading statement with respect to manufacturer, country of manufacturing, country of origin, marketing authorization holder or steps of distribution.
(d) This refers to all components of a medical product.

**WHY DO COUNTERFEIT MEDICINES EXIST?**

The main reason behind this business is the huge profits and high demand for drugs. For counterfeiters, cost of ingredients is low because they use less, use cheap substitutes or totally omit them, as often happens. Production does not require the construction of large infrastructure or facilities, it can be done in cottage industry, patios and warehouses without proper sanitation. There are no costs for quality assurance or compliance with Good Manufacturing Practices (GMP), taxes are not paid and as a result margins are very high in a market of $60 billion USD. (15)

The lack of Good Distribution Practice of human and veterinary...
Counterfeits in Legitimate Supply Chains

Map of Pfizer counterfeited medicines found in distribution chains in different countries (18)

medicines facilitates the entry of counterfeit drugs in the distribution chain. WHO estimates that:
• only 20% of countries have well-developed systems of pharmaceutical regulation;
• 50% have varying degrees of effectiveness in regulating drugs;
• the remaining 30% have a shortage of regulations to control drugs or no compliance is required. (19)

DISTRIBUTION ROUTES
Some countries tend to control pharmaceuticals for export less than the medicines consumed locally.
Free zones are also less controlled and become an opportunity for the illegal drug market.(20) Today the complex trade routes, where products go through several zones and dozens of countries, makes it difficult to determine the exact origin of a coun-

Often the counterfeit medicines “wander” through several countries (sometimes dozens) before reaching their final market. (22)
Counterfeit medicines. As there is a trend towards complex global trade routes and the use of free zones due to their fiscal and logistical benefits, options for inserting illegal goods in the supply chain of any country are many and easy. (21)

EXTENT OF THE PROBLEM

There are no accurate data to measure the extent of this vast, sophisticated and lucrative business accurately, but we are talking about large quantities of drugs seized in various parts of the world. “There is a flow of products coming from everywhere and going to everywhere, there are so many hubs”, says Aline Plançon Interpol officer. (23)

The most reliable sources of data on counterfeiting are the WHO and the International Medical Products Anti-Counterfeiting Taskforce (IMPACT). It is estimated that in developed countries (EU, USA, Canada, Australia, New Zealand and Japan), less than 1% of medicines sold are fake, while in less developed countries this figure is above 10%. In some countries of Africa, Asia and Latin America, the counterfeit drugs may account for more than 30% of the market. In internet it is considered that 50% of the medicines sold are fakes. (19, 20, 24)

The graphic shows some stability in the number of new cases of counterfeit drugs found in the US market until 2000 and exponential growth after 2001 (graphic 1).

In 2009, 20 million pills, bottles and bags of fake and illegal drugs were seized in a five-month operation coordinated by the International Criminal Police Organization (Interpol) through China and seven Southeast Asian neighbors; 33 people were arrested and 100 sales outlets closed. (23)

In Europe, customs officials seized 34 million counterfeit pills in just two months in 2009, Guenter Verheugen Commissioner of the European Union said it “exceeded our worst fears.” (23)

In 2008, in Egypt counterfeit drugs worth hundreds of millions of dollars were found and a network that supplied to consumers across the Middle East was deactivated. (23)

A major concern for the entire Asian region is the high prevalence of counterfeit drugs against malaria. (Antimicrobial resistance in developing countries) The highest prevalence was reached in Southeast Asia and the Mekong Delta, where various studies suggest that between 38% and 68% of the market consists of fake and absolutely useless artesunate. (27)

Asia shows the highest incidence, since it is producer and consumer of counterfeit medicine. In Europe and North America counterfeit drug detection shown is the result of tight control methods in their health systems. In other regions, such as Latin America and Africa it is possible that there are more problems of counterfeit medicines and the figures are higher than those shown above, because the regulatory agencies are more permeable and there are less stringent regulations.
The graph below shows according to the Wall Street Journal some of the biggest captures of counterfeit medicines.(29)

Until recently, the trend was that in developed countries especially the “lifestyle” (weight loss and erectile dysfunction drugs, vitamins, etc.) medicines were falsified. Today these differences are being erased and any counterfeit medicine appears in any country. (30)

Tables 1 and 2 show counterfeit medicines detected in legal and illegal distribution chains worldwide.

There are references to forgery of non-pharmaceutical medical products as well: (20)

- In 2004 in France, regulatory authorities detected counterfeit contact lenses after receiving complaints from patients.
- In 2006 in USA, counterfeit strips for detection of blood glucose were found.
- In 2007 in the UK, 10 cases were reported of counterfeit condoms, difficult to distinguish from the genuine article, but poor in terms of quality and performance.
- From 2009—2013, 7 incidents involving many doctors and many cases were reported of false IUDs (intrauterine devices). (32)

**Consequences**

Needless to say, the serious consequences in economic losses and material resource expenses that this scenario implies for pharmaceutical companies, drug distributors, health authorities and governments in general, and although somewhat different, for patients, whose lives are endangered.
Table 1. Counterfeit medicines detected in the legal distribution chain of Great Britain that were recalled (31)

<table>
<thead>
<tr>
<th>Date</th>
<th>Product</th>
<th>Batch number</th>
<th>Alert</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 2009</td>
<td>Seretide 250</td>
<td>1183R - 06/2009</td>
<td>EL(09)A/12</td>
<td>GB distribution chain</td>
</tr>
<tr>
<td></td>
<td>Evohaler 8mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>June 2007</td>
<td>Plavix 75mg</td>
<td>3103/1 to 3103/20</td>
<td>EL(07)A09</td>
<td>GB distribution chain</td>
</tr>
<tr>
<td></td>
<td>Casodex 50mg</td>
<td>65520 - 07/2011</td>
<td>EL(07)A08</td>
<td>GB distribution chain</td>
</tr>
<tr>
<td>May 2007</td>
<td>Plavix 75</td>
<td>3098 - 08/2008</td>
<td>EL(07)A07</td>
<td>GB distribution chain</td>
</tr>
<tr>
<td></td>
<td>Zyprexa 10mg</td>
<td>A200127 - 02/2009</td>
<td>EL(07)A06</td>
<td>GB distribution chain</td>
</tr>
<tr>
<td>July 2006</td>
<td>Lipitor 20mg</td>
<td>004405K1 - 11/2007</td>
<td>EL(06)A/16</td>
<td>GB distribution chain</td>
</tr>
<tr>
<td></td>
<td>Propecia</td>
<td>243828, Exp: 06/2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>February 2006</td>
<td>Viagra</td>
<td>2183401, Exp: 10/2008</td>
<td>No alert issue</td>
<td>Illegal distribution chain</td>
</tr>
<tr>
<td>September 2004</td>
<td>Reductil 15mg</td>
<td>65542 - 01/2007</td>
<td>EL(04)A/08</td>
<td>GB distribution chain</td>
</tr>
<tr>
<td>August 2004</td>
<td>Cialis 20mg</td>
<td>A041410 - 06/2006</td>
<td>EL(04)07</td>
<td>GB distribution chain</td>
</tr>
</tbody>
</table>

Table 2. Other counterfeit drugs detected in different countries (31)

<table>
<thead>
<tr>
<th>Date</th>
<th>Product</th>
<th>Batch number and expiry date</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 2013</td>
<td>Gentamicin 80mg iny Biviol</td>
<td>L12020299 Exp: 03/2015 920569</td>
<td>Guatemala distribution chain</td>
</tr>
<tr>
<td></td>
<td>Postinor 0.75mg</td>
<td>T13073C, T54365E, T99128L, T12104B</td>
<td>Germany distribution chain Illegal distribution chain</td>
</tr>
<tr>
<td>July 2013</td>
<td>Postinor 2 levonorgestrel tablet, 0.75mg Sulfadoxina 500mg/ Pirimetamina 25mg Sutent</td>
<td>T13073C, T54365E, T99128L, T12104B</td>
<td>Nigeria distribution chain Illegal distribution chain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1833, Exp: 02/2014</td>
<td>Nigeria distribution chain</td>
</tr>
<tr>
<td>June 2013</td>
<td>Cialis 20mg</td>
<td>05668</td>
<td>Illegal distribution chain</td>
</tr>
<tr>
<td></td>
<td>Viagra 100mg</td>
<td>B314833021</td>
<td>Illegal distribution chain</td>
</tr>
<tr>
<td>May 2013</td>
<td>Suustanon 250</td>
<td>3CSH550</td>
<td>Illegal distribution chain</td>
</tr>
<tr>
<td>March 2013</td>
<td>Omeprazole 20mg</td>
<td>BZ4333 E008 E018 G003</td>
<td>Germany distribution chain</td>
</tr>
<tr>
<td>February 2012</td>
<td>Altuzan 400mg/16mL</td>
<td>B0621, Exp: 10/2012</td>
<td>USA distribution chain</td>
</tr>
<tr>
<td>April 2011</td>
<td>Cialis 20mg</td>
<td>05668, Exp: 04/2013</td>
<td>Illegal distribution chain</td>
</tr>
<tr>
<td></td>
<td>Viagra 100mg</td>
<td></td>
<td>Illegal distribution chain</td>
</tr>
</tbody>
</table>

* Warning: this code can be searched online
Counterfeit medicines exist since time immemorial. Now they have turned into a far greater scourge, since it has become a very lucrative business, easy to carry out and with relatively few restrictions. The trend is for the market of counterfeit drugs to increase every year.

There is no simple solution or a standard for all countries to eliminate this problem. Each country has to develop a strategy based on its particular situation, taking into account the available infrastructure and human resources.

Drugs that are most likely to be falsified are those from international laboratories with great market demand and high cost, which guarantee a high volume of business with attractive prof-

• In Singapore in 2008, 150 people were admitted for severe hypoglycemia; four of them died and 7 suffered irreversible brain damage. They had used erectile dysfunction pills containing glyburide. (20)
• Between 2007 and 2008, a contaminated blood thinner, heparin, was linked to 149 deaths in the United States. (34)
• In October 2012, contaminated steroids near Boston, USA, killed 11 patients by fungal meningitis and more than 100 became sick. (34)
• In 2012, some vials of the cancer drug Avastin did not contain any active ingredient. (34)
• In Belgium and Germany, counterfeit heparin possibly led to 81 deaths and hundreds of side effects in patients.
• In December 2004, in Argentina, a 22 year-old pregnant woman with slight anemia died of liver failure after receiving injections of a counterfeit iron supplement in a public hospital. Two other women also died after receiving the counterfeit product and a dozen other women were less affected. (35)
• During a meningitis epidemic in Niger in 1995, more than 50,000 people were inoculated with fake vaccines that caused 2,500 deaths. The vaccines were a gift from a country that considered them to be genuine. (36)
• In Haiti, in 1995, 89 children died and 30 more children died in India in 1998, due to ingestion of cough syrup with acetaminophen made with diethylene glycol (a toxic chemical used as antifreeze substance).

Limitations
This review presents only some data extracted from the literature, however, this problem is large when you consider:

• Lack of information on counterfeit drugs that exists in all institutions involved in the production, distribution and use of drugs.
• A dynamic market that adjusts to patients’ tendency to get more economical products, with total unawareness of the consequences to their health.

Conclusions
Counterfeit medicines exist since time immemorial. Now they have turned into a far greater scourge, since it has become a very lucrative business, easy to carry out and with relatively few restrictions. The trend is for the market of counterfeit drugs to increase every year.

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In Belize, the Ministry of Health is already working on the organization of a pharmaceutical registration. It has established a system of pharmacy inspections to ensure better control of the distribution and use of medicines in the country. However, everyone involved in the health system (importers, distributors, doctors and pharmacists) are responsible for providing reliable, safe and effective medicines to the population.

Public health is everyone's responsibility; nowadays, the ease with which we travel from one point to another of the planet makes us more vulnerable and we must be prepared, it is essential to have the right medicines to meet any emergency.

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