Counterfeit drugs in industrialized and developing countries – A comparison

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Für meine Familie, meine Freunde und Hagbard Celine.

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List of abbreviations

AGES	Agentur für Gesundheit und Ernährungssicherheit
API	Active Pharmaceutical Ingredient
BKA	Federal Criminal Police Office
DG TAXUD	Directorate-General Taxation and Customs Union
DRA	Drug Regulatory Authority
EFPIA	European Federation of Pharmaceutical Industries and Associations
FDA	Food and Drug Administration
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
IMPACT	International Medical Products Anti-Counterfeiting Taskforce
INTERPOL	International Criminal Police Organization
MHRA	Medicines and Healthcare products and Regulatory Agency
OMCL	Official Medicines Control Laboratory
OTC	Over the counter
PSI	Pharmaceutical Security Institute
WHO	World Health Organisation

Introduction

Counterfeit drugs have a long history. As early as 400 B.C. there have been warnings of their presence and Dioscorides, a Greek physician, pharmacologist and botanist 40 – 90 A.D., wrote in his 'Materia Medica' about the detection of counterfeit drugs. (1) (2)
The threat of counterfeit medicines therefore hardly is a new one and it persisted through the ages. The 'modern' issue of counterfeit medicine emerged in the 1980s when more and more member states of the World Health Organisation (WHO) reported counterfeit medicines. It was first brought to a greater attention on an international conference on the rational use of drugs in Nairobi 1985. In 1988, the WHO was requested to work on the growing problem of counterfeit medicines. (3)

Before going into the details associated with counterfeit medicines a solid definition of the term should build the basis of this work.

What are counterfeit medicines?
In general, several different forms of counterfeit medicines can be distinguished.

They might contain:

- no active pharmaceutical ingredient (API) at all,
- incorrect amounts of the correct API,
- incorrect APIs, sole or in mixtures
- or API in the correct amount but with fake packing, labelling and patient information leaflet.

To include all these possible and different types of counterfeit medicines a definition of the problem was made on the initial international meeting on counterfeit medicines in 1992 and an updated and broader definition has been found during the third general IMPACT meeting in Tunisia in 2008. (3) (4)

The WHO definition is:

> 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 labelling 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 behaviour 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.

Aim and Methods

Counterfeit medicines are present in industrialized and developing countries. The extent of the problem and several other factors concerning the counterfeited drugs however differ significantly between industrialized and developing countries. E.g., the market share of counterfeit drugs is below 1% of the total medicines market value for countries like the USA, Japan or the EU. In contrast, this number can reach over 30% for parts of Africa, Asia and Latin America according to WHO data. (5)

The aim of this master thesis is to present a current, compact and accurate view on the problem of counterfeit drugs on a worldwide basis. It should especially address and list the differences of the problem in industrialized and developing countries to be able to make a comparison between them. It should furthermore address the reasons of these differences.

Points to be considered in this thesis include:

- The reasons why counterfeit drugs exist
- The extent of the problem
- Place of production (Which drugs are counterfeited where?)
- The Distribution channels
- Consequences of counterfeit medicines
- Are there trends and developments to the points mentioned above

The data and information used in this master thesis will be gathered from primary sources like the WHO or Food and Drug Administration (FDA) website and other official publications and secondary sources like articles published in journals, newspapers and further web based sources. The countries described have been chosen because of relevance and availability of data. All sources are given directly in the text or in the reference chapter.

Many Stakeholders, many points of view

In the following work a lot of numbers will be presented. However these are to be read with care. The counterfeit business as a whole and the counterfeit medicines business in particular are illegal businesses and therefore done subsurface and in secret. That of course makes finding exact numbers challenging.

This problem is furthermore elevated via different aspects, including:

- **Many sources of information**
  These come from different stakeholders, e.g. the pharmaceutical industry, national authorities or nongovernmental organisations, with different point of views. Also some of these sources only share very little information for different reasons.
- **Different definitions of counterfeit medicines used by the different stakeholders**
  The numbers given in the following chapters are based on the definitions used by the concerned stakeholders.
- **A lack of awareness**
  This can exist on all levels in the drug chain (pharmaceutical industry, health authorities, pharmacies, health professionals and the patients) and leads to the non-detection of counterfeits.
- **A fluctuating market**
  The counterfeits medicines market is rapidly changing, therefore the findings of today can be out-dated tomorrow.

Hence the numbers given in the following chapters should not be taken as exact facts but rather as estimations of a fast changing and highly illegal market.

Why do counterfeit drugs exist?

The reasons for counterfeit medicines are manifold and diverse. A criminal interest combined with extremely high possible gains, weak or absent regulations and authorities, consumers seeking the cheapest medicines and missing attention to a more than serious problem to name only a few.

This chapter will give an overview of these reasons.

Insufficient or missing regulations (1) (6)
Without the proper regulation of all aspects concerning the manufacture, the distribution and the sale of drugs the health market of a country cannot be secured with regard to counterfeit medicines.

According to the WHO (1) these regulations should include several points.

- Manufacturers and importers of APIs and / or finished drugs should need a license for production or importation.
- The further supply chain for distribution and sale to the customer should also be subjected to licensing and inspections.
- Inspections of these manufacturers or importers should be possible.
- Before drugs enter the market, either through local manufacturing or through importation, they should need an authorisation.

The problem of insufficient or missing regulations is wide spread. The WHO estimates that 30 % of all countries are missing drug control regulations or cannot enforce them whereas only 20 % have well developed drug regulation systems. The remaining 50 % show varying degrees of effectiveness and regulation. (7)

The problem is even worse when taking a specific look at the African countries. Whereas 54 % have no quality monitoring program for drugs only 19 % have one implemented at all. 77 % of the analysed countries had no regulation concerning product recalls, so even if counterfeits are detected not much can be done. Only 5 of the 26 countries in the WHO report conducted inspections as anti-counterfeit effort. (8)

Also the situation in Africa as described above is very serious other parts of the world also show their deficiencies. An example of existing but insufficient regulations is given by the Ukraine. Here import and export of counterfeit goods is prohibited under the Customs code, however their destruction is not regulated and the goods, including counterfeit medicines, often find their way back to the market. (9)

Insufficient or missing authorities

The regulations mentioned above have to be enforced on the market. To achieve this it is vital to have a working and effective authority in place asserting the necessary controls on new drugs before they are allowed to enter the market, on the local manufacture and the importation of drugs as well as on the distribution chain for pharmaceutical goods. A lack of such an institution will lead to a flourishing illegal market for counterfeit drugs.

Furthermore, the relevant authority also needs to have backup by suitable analytical laboratories to be able to detect counterfeits.

India for example, although it is one of the world leading countries in terms of manufacture of pharmaceutical goods, is parted in states and territories. Of these 31 parts only 17 have functional laboratories for drug testing and only 7 of these are sufficiently equipped. An overall national Regulatory Authority is missing. (10)

Another prime example of insufficient quality laboratory control is the malaria affected sub-Saharan part of Africa where only two WHO pre-qualified laboratories exist. (7)

More developed countries also suffer from insufficient authorities. Russian authorities with 700 local drug manufacturers, 7,000 distributors, and 70,000 pharmacies to monitor stated that they cannot maintain sufficient controls and named this as the main reason of the high prevalence of counterfeit drugs in their country. (9)

Insufficient law enforcement and insufficient penalties

As well as missing regulations and weak authorities will lead to the prospering of undesired counterfeit activities, insufficient law enforcement and insufficient penalties will lead to this effect. If counterfeiters are not persecuted, may it be through corruption, because of insufficient resources, or if penalties are too low for deterrence, they will continue their trade. (11) (12)

High prices and a disparity between supply and demand

High prices affect the prevalence for counterfeit drugs on two ways. First patients will tend to look for cheaper drugs and will rather be open for less trustworthy sources of the drugs they need. (11)

On the other hand a high drug price is of course a major incentive for counterfeiters.

The same holds true for goods where the demand is higher than the supply, besides the fact that the price of the goods in question will also rise.

The major example for counterfeit medicines, Viagra® and similar products clearly underline this point. As the demand is high but unmet due to the prescription status, the price and further reasons, customers tend to buy it from the grey and black market, leading to a very high risk of receiving counterfeits.

Unmet demand is also a problem of especially rural areas in developing countries where official, legal channels cannot satisfy the customer needs in regards of pharmaceuticals. (13)

One example is Burkina Faso where, despite the national regulations demanding prescription for all drugs, people tend to buy from illegal but cheaper street vendors where, according to official sources, one in five drugs is counterfeit. (14)

Besides the price the availability of drugs is also a problem in most sub-Saharan countries, where illegal street vendors sometimes are the only source for pharmaceuticals. (15) (16)

Complex trade routes, importation, exportation and the problem of free trade zones

The more complex a trade route is, the easier it is to comprise and to insert counterfeit drugs. As a tendency towards more complex and more global trade routes persists, the options for counterfeiters to insert their illegal goods into the supply chain rise. (17)

Distribution to the customer can be another problem, especially in less developed countries where single blisters or even single pills are often sold by non-specialists, counterfeits are inevitable and hard to detect without even the most basic information like producer dates, any batch number or the expiration date. (14) (15) (16)

For example 40 % of the finished drug forms and 80 % of the APIs used in the USA are imported from overseas. Of course this foreign production and the distribution chain are much harder to control than locally produced goods. (18)

On the exporting side some countries tend to control the pharmaceuticals for exportation to a lesser degree than the locally consumed drugs. (19) Free trade zones as a special part of the trade routes also tend to be less controlled than the rest of the territory of a country and therefore open special opportunities for the illegal market.

Higher quality – less detection

As the techniques in the legal pharmaceutical business evolve, so do the techniques in the counterfeit business. With high quality equipment for the production of counterfeit goods, packaging and labelling, the counterfeits become harder and harder to detect especially for patients and prescribers. (19) (20) Often only highly developed methods like detailed chemical analysis or x-ray refraction will reveal the counterfeit. (21) (22)

This can consequently lead to a higher prevalence of fake drugs, especially in the legal supply chain.

Cooperation of different stakeholders

It has been mentioned earlier in this work that there are a lot of different stakeholders affected by the problem of counterfeit medicines. These include the legitimate pharmaceutical industry, different authorities like police, customs, the national Drug Regulatory Authorities (DRA) or health professionals and patients. (19) (23)

When the cooperation between these stakeholders is poor, e.g. the industry hesitates to inform the authorities of their findings, this will have massive effects on the safety of the pharmaceuticals market.

Reasons on the supplier side include the fear that detected and publicly announced counterfeits will also negatively affect their brands. There is furthermore the potential problem that the consumer will stop to take their (non-counterfeit) medicines for fear of counterfeits. (12) (23)

High profit margin

High profit margins are to be made in the counterfeit drugs business even in comparison to other 'branches' of the illegal black market. The production of counterfeits is feasible without large infrastructure and even possible in homes or backyards. Also the 'raw materials' are rather cheap when counterfeiters are willing to risk consumer's life's and neglect all quality assurance and product safety and sterility issues normally connected with pharmaceutical production.

Profits are high: e.g. for 1,000$ investment counterfeit money returns 3,300$, counterfeit credit cards 6,700$, heroin 19,860$, counterfeit cigarettes 43,000$ but counterfeit drugs return up to 500,000$. (24)

The margin is also higher when you look at the per kilo price; whereas a kilogram of heroin brings in 65,000€, the same amount of fake drugs earns in 90,000€.

Therefore the counterfeit drugs business is even more profitable than illegal drugs and at the same time holds fewer risks for the criminals. (12) (25)

The Internet

The Internet offers many opportunities to criminals willing to exploit them. It is possible to disguise the real identity, to easily reach a large amount of potential customers with mass spam emailing, to present yourself as a legal Internet pharmacy and to act globally.

Patients, foremost in developed countries, seek an easy, prescription free way to cheap, maybe stigmatized or even illegal medicines.

This combination leads to a high degree of counterfeits in the illegal Internet market. (26)

Lack of awareness by stakeholders

This lack of awareness can include health professionals as well as patients and leads to a very low amount of reports of counterfeit drugs from their side. (19) (23)

This is based, at least to some degree, on the low amount of information delivered by pharmaceutical industry and also governments.

Counterfeit in numbers

This chapter will concentrate on the prevalence of counterfeit drugs in different countries and regions of the world. As the dimension of the counterfeits market remains unclear, for the reasons already mentioned, the figures here are estimates given by different sources.
The most important sources for data on counterfeits are the WHO and International Medical Products Anti-Counterfeiting Taskforce (IMPACT) as the WHO's organisation for the fight against counterfeit drugs.

For some years the estimation of the global prevalence of counterfeit drugs has been 10 % overall.
This rather rough estimate has been split into a more detailed picture in 2006 and the following years when IMPACT gave single figures for different world regions along with data for single countries which will be presented later in this chapter.

The new estimates differentiate between developed countries, including the EU with the exemption of some of its most eastern parts, the USA, Canada, Australia, New Zealand and Japan, where less than 1 % of the drugs sold are counterfeit and a number of over 10 % for some less developed countries. For some of these countries in parts of Asia and Latin America the estimations go further up above 30 %. In a lot of countries of the former Soviet Union counterfeits reach a prevalence of over 20 % according to the WHO assumptions.
A much higher prevalence can be found in drugs bought on illegal Internet pharmacies, where up to 50 % of the sold medicines are assumed to be fakes even in developed countries.
However the differences are not supposed to be only huge between developed and less developed countries or between different world regions, they can also differ significantly in a single country between different cities or cities and rural areas. (5) (13) (26)

Other sources give similar alarming numbers. For the time between 2000 and 2006 the numbers of counterfeits are estimated to have grown 800% and to continue to grow with an annual rate of 13% through 2010 resulting in a market of over $75 billion, an increase of over ca. 90 % in comparison to 2005 numbers. This would be a market share of around 15 % in comparison to the legal pharmaceuticals market. (20) (27) (28) (29)

EU

In comparison to less developed regions the amount of counterfeits in the EU supply chain remains still very low. Between 2001 and 2005, 27 cases have been detected in the legal supply chain and 170 were detected in its illegal counterpart according to an EU Working Group of Enforcement Officers 'survey.

The Directorate-General Taxation and Customs Union (DG TAXUD) however reported in 2007 a rise of seizures of counterfeited drugs for the two previous years of 384 % to a total number of 2 711 410 single goods in 2006, so one can assume that these low numbers found in the supply chain will rise in the near future. (30) (31)

In 2006, the share of counterfeited medicines rose to 2 % of the total seized counterfeits, showing the growing importance of fake drugs for criminals in the counterfeit business. (32)

During a combined operation of different European authorities 34 million counterfeit tablets could be confiscated in only two months (28) (33) showing together with other sources (21) that the still high security of the European pharmaceuticals market is threatened by counterfeits.

As stated above, the former Soviet states show a significantly higher rate of counterfeits on their markets. It has been feared that the association of the Baltic States with the EU will raise the prevalence of counterfeits in the EU. (29)

DE

In Germany the legal supply chain is rather secure. Between 1996 and the middle of 2009 only 40 cases have been detected according to Bundeskriminalamt (BKA, German Federal Criminal Police Office) information. (6)
The presence of counterfeit drugs in general is on the rise. Whereas in 2006 fake drugs worth 2.5 million € could be seized by German customs counterfeit medicines worth 8.3 million € in 2400 cases could be seized in 2007. (32) Other sources also point to a growing market for counterfeits in Germany. The German customs reported a 58 % rise of investigations concerning counterfeit drugs between 2008 and 2009 alone. (34)

UK

In UK up to date nine recalls had to be made since 2004 because counterfeit drug batches reached the patient level. Five further cases were detected at the wholesalers-level in the same time. (21) (35) (36) This means a clear increase in comparison to one single incident in the previous decade to 2004. (21) Seizure by the British customs also rose significantly in 2006 to 497 cases with 2.7 million counterfeits which is a fourfold increase compared to the numbers of 2005. (12)

Bulgaria

The general rise in counterfeit numbers is also visible in Bulgaria where the case number grew from 5 in 2005 to 15 in 2007. (21)

AT

Austria, like other developed countries, shows a sharp rise in the counterfeit cases and the number of seized fake drugs. The following graphic based on data from the Austrian customs shows the number of cases and seized counterfeits between 2004 and 2007. The cases rose from 0 in 2004 to nearly 1000 in 2007 and the seized goods from 0 to 42,386 (see figure 1). The real numbers may even be considerably higher as the numbers given above only include the goods seized for copyright infringement, together with smuggled goods, that often are counterfeits numbers, sum up to 30,000 in 2006 and 224,000 in 2007. (24)

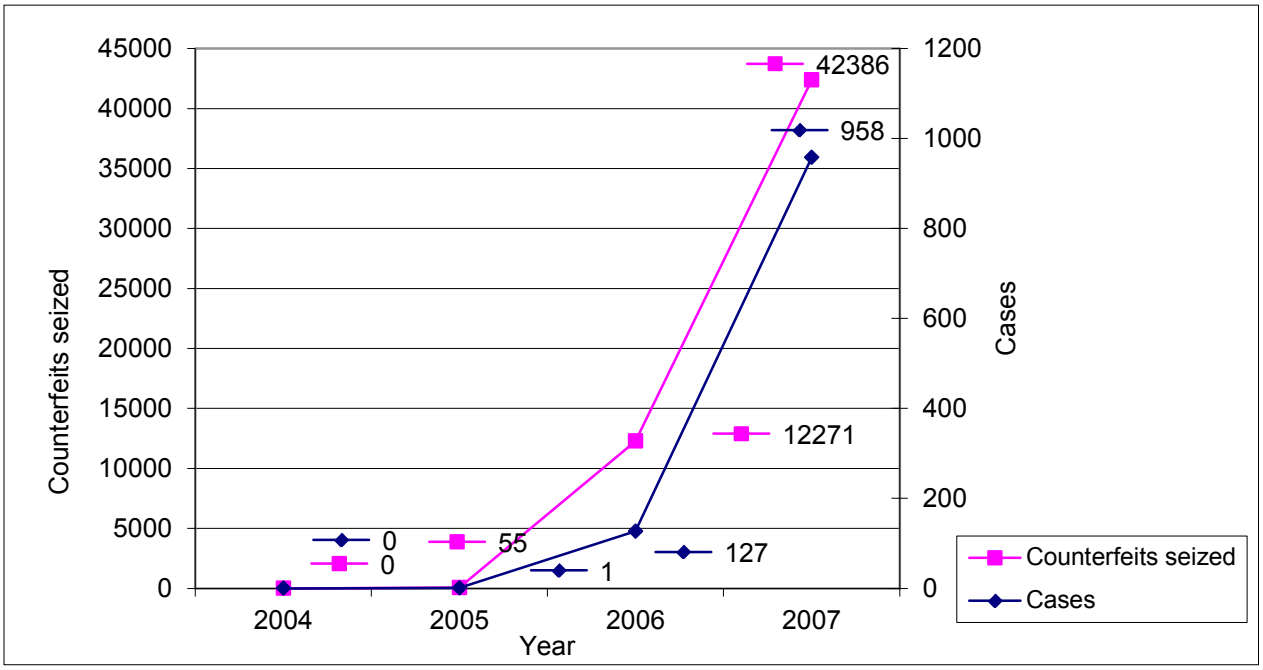


Figure 1: Overview 2004 – 2007 for counterfeit medicines cases and counterfeit drugs seized by Austrian customs. Data derived from (24)

Russia

The Russian Federal Service for Health Sphere Supervision places the number of counterfeits at 10 % of the total pharmaceuticals market in Russia. A counterfeit share between $ 300 - 400 million of the ca. $4.5 - 5 billion pharmaceuticals market has been estimated for 2004. The Coalition for Intellectual Property Rights gives a slightly higher number of 12 %. (5) (9) (14) (29)
Counterfeits worth $600,000 have been seized in Russia in 2003 alone. (9)

Ukraine

The prevalence in the Ukraine seems to strongly depend on the stakeholder involved. The official numbers given by the Ukrainian State Inspectorate for Quality Control of Medicines reported a rate of 0.33 % of counterfeits after conducting a study in 2004. Other sources come to a different conclusion and give numbers of 40 % for the total market and 80 % for certain medicines.
The Ukrainian counterfeit drugs market in total has been believed to be worth $60 million in 2005. (9)

US

Whereas the amount of seized fake drugs in 2003 has been $200 million for 2008 the value of the counterfeits market in the USA has been estimated to be $39 billion in total. (14)

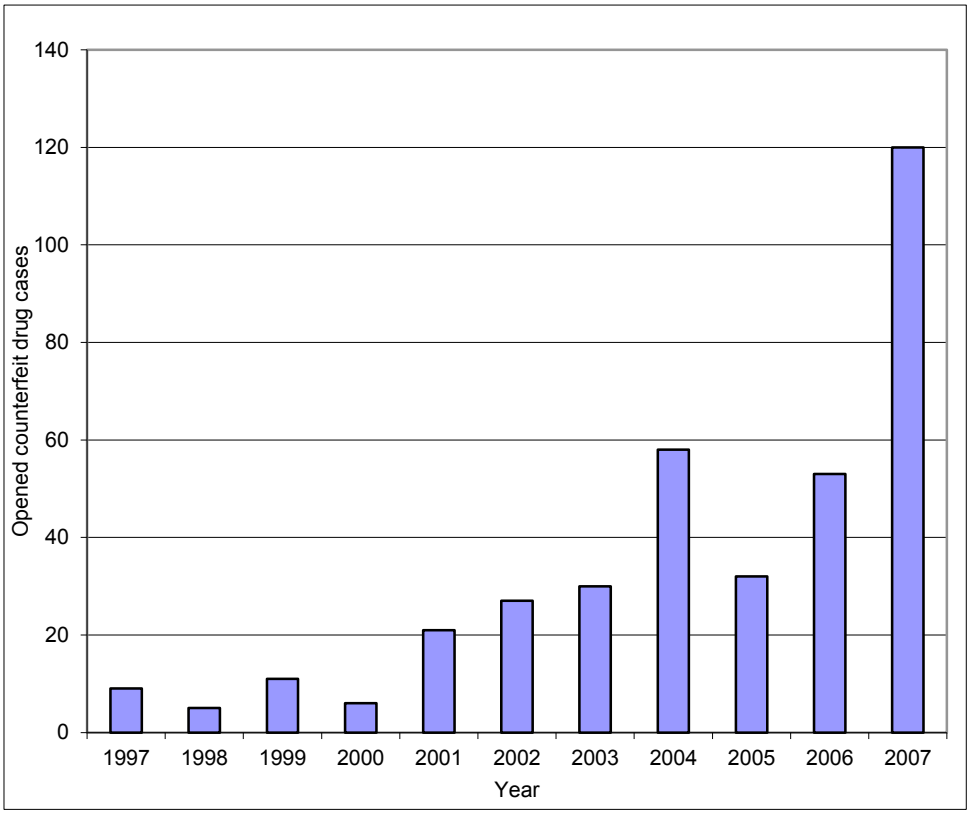


Figure 2: Overview of US FDA opened counterfeit drug cases from 1997 to 2007. Data derived from (14) (17) (21) (37).

The counterfeit drug cases opened by the US FDA were stable at around 5 cases per year at the end of the 1990s. This number saw a clear trend to raise beginning in 2000. A maximum had been reached in 2007 where 120 cases were reported (see figure 2). (14) (17) (21) (37)

Latin America

Estimates for Mexico give a rate of 10 % counterfeits in the pharmaceuticals market, with a tendency to grow.
For the Dominican Republic the Public Health Department gives numbers of 10 % for the counterfeits share with imports. (5) (14)

Asia

A major concern for the whole Asian region is the high prevalence of counterfeit anti-malaria drugs. (14) (23)
A peak in this prevalence is reached for South-East Asia and the greater Mekong Delta where different studies and reports suggest that between 38 % and 68 % of the Artesunate, on the market, used as treatment for malaria, is counterfeit and mostly useless. (6) (28) (38) (39) (40) (41)
India not only is one of the biggest producers of counterfeits as will be shown in the following, it has also a huge market for medicines and counterfeits. It is estimated by Indian pharmaceutical companies that 20 % of all drugs sold are fakes. (5) However India, due to its size and the different regulations in the different states, cannot be seen as a single country, the prevalence in its single sub states is estimated to range from 5 to 30 %.
According to Indian Health officials however the prevalence for counterfeits is only 1 % of the Indian Market. (14)
Pakistan shows an even higher rate. The European Federation of Pharmaceutical Industries and Associations (EFPIA) gave a number of 50 % of the complete market and estimates similar numbers for the markets in China and Nigeria. (29)
A study conducted by the Cambodian Health Ministry in 2002 showed that 13 % of the medicines sold were either substandard or counterfeit. (5)

For China 8 % fake drugs are estimated for the Over the counter (OTC) market. (5) (14) That alone is a huge number taking into account the size and the population of china.
The Chinese authorities reported 480,000 cases involving counterfeit drugs for 2001 alone. (20) (23)
Indonesia has to struggle with a counterfeit drug prevalence of 25 % according to the International Pharmaceutical Manufacturers Group, this would mean a $ 500 million share of Indonesia's $ 2 billion medicines market. (5)

Middle East

For the Lebanon the Lebanon, its National Health Commission reported in 2004 that 35 % of the drugs in the pharmaceutical market are counterfeits. (5)

Africa

Africa shares some problems with Asia in terms of counterfeit drugs. Especially the situation concerning anti- malaria drugs resembles the situation in Asia. (14)
For example for a certain subgroup of these medicines, Artemisin and its derivatives like Artenusate, a study found that around 33% of all dosage forms and 77 % of the injectable dosage forms were fakes in the DR Congo and in Kenya. (12)
Before 2006 Nigerian health officials believed that ca. 70 % (40 - 50 % according to other sources) (42) (43), of the medicines market was composed of counterfeits. Due to the efforts of the National Agency for Food, Drug Administration and Control (NAFDAC) this estimation dropped to 'only' 16 % from 2006 on. (5) (42)
This drop in the prevalence has been accompanied by the seizure of counterfeits worth $100 million between 2001 and 2006. (20)
In Kenya a study performed by the National Quality Control Laboratories (NQCL) and the Pharmacy and Poisons Board found nearly 30 % counterfeits in the medicines supply. Counterfeit sales have an estimated value of $130 million in Kenya. (5) (44)

For the Senegal no estimates for the complete market were available, however a study conducted in 2002 reported that for ampicillin, one of the basic antibiotics, 21 of 22 samples were counterfeit, a rate of over 95 %. (14) (44)

The situation in Cameroon has been evaluated by an U.S. Pharmacopeia study. It found that 39 % of all samples were counterfeit. (14)

For Angola the National Department of Intellectual Copyright Crime of the Economic Police estimates that, as in pre-2006 Nigeria, around 70 % of all drugs available are fakes. (5)

What drug is counterfeited where?

Viagra® is without any doubt the most famous counterfeited medicine in the western world. However the counterfeit business is by no means restricted to this certain drug. Generics are affected as well as innovative patent medicines, high cost drugs as well as relatively cheap mass market pharmaceuticals. (45) (46)

Fake medical devices like counterfeit condoms, blood glucose test strips or contact lenses and many others are also present on the markets (26)

There are certain primary targets for the counterfeiters when it comes to terms of pharmaceuticals classes.

The two following figures 3 and 4 with data from the WHO show the distribution of different pharmaceuticals counterfeited. While the data behind both figures were published by the WHO they also show that the absolute numbers depend on the point of view of the concerned stakeholder, as described in the chapter 'Many Stakeholders, many points of view'. (19)

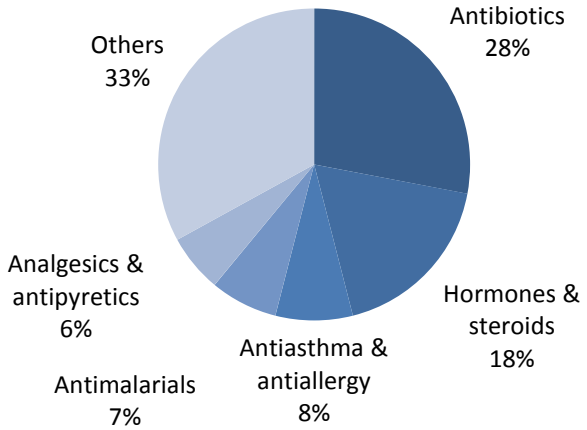


Figure 3: Pharmaceutical classes of counterfeits reported to the WHO between 1999 and 2002. Data derived from (19).

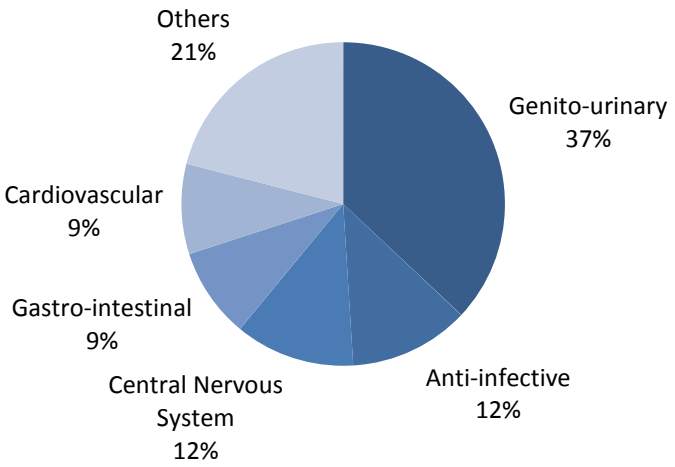


Figure 4: Pharmaceutical classes of counterfeits reported to the Pharmaceutical Security Institute between 2007. Data derived from (19).

Developed Countries

In general in developed countries, so called 'lifestyle' drugs, e.g. for the treatment of erectile dysfunction, anabolic substances and medicines for weight loss, often sold over the Internet, made up the biggest share of counterfeited pharmaceuticals. (28)
While they still account for a major share, other medicines are on the rise. These lifesaving medications include anti-cancer drugs, medicines against cardio-vascular diseases, psychiatric disorders and antibiotics.
For the less developed countries, counterfeited lifesaving medication in many pharmaceutical classes has been reported. A big share is made out of anti-infective drugs of all kinds. (14)
Besides counterfeits from Internet mail order, also including total counterfeits, fake drugs in the more developed countries are often re-packaged original medicines that have been illegally re-imported. (47)

EU

Although the prevalence of counterfeited drugs in Europe is relatively low compared to less developed regions in the world counterfeits, both in the legal and in the illegal supply chain, are present.
Even though 'lifestyle' drugs are the most prevalent, a few examples showing the range of different classes of other drugs are given in table 1 below.

Counterfeit medicine	**Country**	**Year**	**Background**
Anti-AIDS drugs	DE	2003	Found in a pharmacy, counterfeit packaging and PIL (14)
Oseltamivir	NL	2006	Sold on the Internet, no API (26)
Atorvastatin	UK	2006	Detected in the legal supply chain, insufficient API (13) (19)
Oseltamivir	UK	2006	Detected by customs (19)
Olanzapine	UK	2007	Detected in the legal supply chain, insufficient API (13)
Oseltamivir	BG	2007	Detected by customs, no API (21)
Antibiotics, anti-cancer, cholesterol lowering, pain-killers, Viagra®	EU	2008	Medicines found during customs operation ‚Medi-Fake' (33)

Table 1: Examples of counterfeit cases in the EU

UK

As in other developed countries the Medicines and Healthcare products and Regulatory Agency (MHRA) reports that the most common counterfeited medicines have been the 'lifestyle' drugs especially for treating erectile dysfunction and for weight loss. However this preference changes towards lifesaving drugs (see table 1). (48)
The counterfeits detected in the UK usually do not have the wrong API or no API but often show a reduced amount of active ingredient. (35) (36)

DE

In Germany especially false presentations of Viagra® and related drugs as well as anabolic steroids and other doping drugs are present. According to the German customs antidepressants, anti-allergy medicines, pain killers and drugs for weight loss can also be found. (34)
Counterfeits in Germany often include the original medicine, often intended for export only, repackaged in fake primary and/or secondary packaging when they are detected in the legal supply chain.
For counterfeits bought illegally, for example anabolic drugs, totally missing API is not uncommon. (49)

AT

Austria reports especially drugs against erectile dysfunction, anabolics and, a special case not commonly reported by other states, fortified homeopathics as counterfeited. From the 463 counterfeits analysed in the Agentur für Gesundheit und Ernährungssicherheit (AGES) Official Medicines Control Laboratory (OMCL) 96 (20.73 %) were anabolics, 97 (20.95 %) drugs against erectile dysfunction and 185 (39.96 %) were homeopathics. (50)

USA

The situation in the USA is similar to that in Europe. While ‘lifestyle’ medication like Viagra® and Cialis® (9) (51) have been the primary target in the past and remains important for counterfeiters there are numerous examples of more essential medicines being counterfeited. With Lipitor® the counterfeiters targeted a commonly used cholesterol-lowering drug several times. (52) Procrit®, Zyprexa®, Serostim® and Neupogen® (9) (51) are only a few of the further examples (19) (23) (48) (53) of this trend towards falsifying lifesaving drugs.

Developing Countries

In contrast to the developed world counterfeits in developing countries are seldom from the ‘lifestyle’ drugs classes and more often from essential and basic medicines classes. However drugs from all classes can be found as counterfeit and the market is not limited to certain specialities.
Antibiotics and especially anti-protozoal drugs against malaria are often reported as counterfeit. (45) Antibiotics are 8-10 times and anti-protozoals 2-3 times more often reported than counterfeits as the other drug classes. (14) (54) (55)
Faked anti-tuberculosis drugs, an antibiotics subclass, and anti-retrovirals used against HIV/AIDS are also commonly known. (15) (54)

Russia

Russia, between the developed and the less developed world, has, thanks to its geographic position, no problems with malaria. Here, the most common counterfeits affect medicines against cardiovascular and gastrointestinal diseases.
The counterfeits are often of a good ‘quality’, containing ‘only’ insufficient amounts of API. (14)

Asia

As already stated above anti-malaria drugs are often targeted by counterfeiters in Asia. Their prevalence goes up to over 50 % in South-East Asia where many different brands are faked. (6) (55) (40)
Counterfeits are however not limited to anti-malaria drugs at all. E.g. other anti-protozoal drugs like Miltefosine, for treatment of leishmaniasis, have been targeted as well as vaccines against influenza, rabies and tetanus. (7)
Fake antibiotics, birth-control pills and pain-killers have been found among other counterfeited drugs. (40)
From the 'lifestyle' drugs especially erectile dysfunction medicines are also not uncommon in Asia. (28) (56)
Counterfeits in Asia are often produced without any API, although other types of counterfeits are also to be found. (41)

Africa

In Africa especially the sub-Saharan part has to suffer from counterfeit drugs, but they are present throughout the complete continent.
Like in Asia fake anti- malaria drugs are a common problem. E.g. Chloroquin is faked in around 50 % of the cases in some African countries, including Angola, Burundi and the DR Congo, and fake Artesunate is also becoming more and more prevalent. (38) (39)
Antibiotics are also commonly counterfeited, as an example from the Senegal shows, where 21 of 22 samples taken of Ampicillin contained flour instead of the correct ingredient. (14)
Another big share of the counterfeits market in Africa falls to anti-retroviral drugs against AIDS/HIV, Stavudine/Lamivudine/Nevirapine and Lamivudine/Zidovudine have been found among others. (57)

Fake vaccines are a further problem, highlighted by a cause in 1995, where during a meningitis epidemic in Niger 88,000 units of meningitis vaccine without API have been given to patients. (23)

However not only counterfeit anti-microbial and anti-viral drugs are present. The whole spectrum of drugs can be found as fakes in Africa including medicines against cancer, pain and diabetes or heart disease and epilepsy. (40) (58)

As it is the case in Asia counterfeits in Africa also often contain no API at all. However the other types of fakes, containing wrong or insufficient amounts of API, are also seen regularly. (44)

The ways of distribution

The production and trade of counterfeit medicines are fast growing businesses. (59)

A trend is seen by different stakeholders, e.g. Interpol, that organized crime is rearranging its priorities from narcotics to the more profitable and less risky counterfeit drugs. (6) (14) (44)

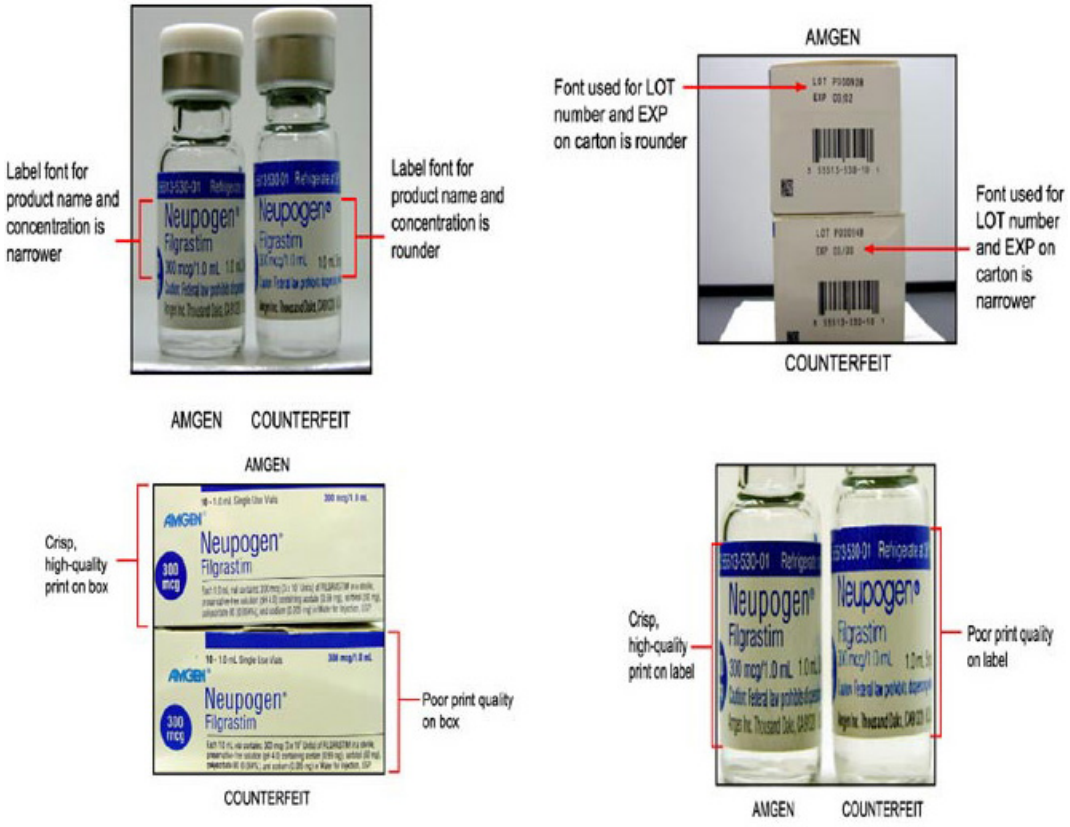
Depending on the 'quality' of the counterfeits it can be a rather cheap and easy crime. If one doesn't care for safe production standards, special infrastructure or facilities are not needed and the counterfeit production can be done in cellars or backyards. (19) It is however not uncommon that counterfeits are produced in 'normal' pharmaceutical factories often in parallel to the legal production. (57)

The industry sponsored Pharmaceutical Security Institute names Asia and in particular India and China and to a lower degree Pakistan and other countries of the Mekong River Valley as the main sources for counterfeit medicines. (9) (10) (12) (28) (42) (44)
It is easy to believe that these countries belong to the biggest sellers of fake drugs, as they are also the biggest sellers of legitimate drugs. Some sources say that up to 90 % of the legitimate drugs used in the western countries have their origin in China. (9)
However illegal productions sites have also been found or at least suspected all over the world from Latin America to Russia. (14)

From the production sites the fakes are often shipped through different free trade zones to disguise their origin and then brought into the target market.

The introduction into the market can be made with different approaches. To breach the legal supply chain either wholesaler or pharmacies have to buy the counterfeit products either knowingly or at least accepting a dubious pedigree. (17)
Exactly this happened for example in 2006 when a US pharmacist planned to sell several thousand fake tablets against erectile dysfunction.
A trend is seen concerning the targeting of the legal supply chain of developed countries. (14) (31) This trend is accompanied by higher quality counterfeits that are hard to detect without chemical analysis because the labelling and packaging, including security details like holograms or barcodes, mimics the original exactly. (17) (42)

The following picture 1 showing original and counterfeit Neupogen® detected in the USA emphasizes this point.



Picture 1: Original and counterfeited Neupogen® in comparison. (17)

Besides the legal (and safer) ways to buy medicines an illegal grey and black market exists for especially prescription or illegal drugs. This can include unofficial pharmacies and street-vendors in the developing countries or the Internet in the developed countries.

The Internet is one of the main sources for counterfeit drugs, especially in the developed countries and for the illegal grey and black market e.g. for Viagra®, anabolics and weight lowering pills. The 'quality' of these counterfeits is even worse than the quality of counterfeits in the legal supply chain. (14) (47) (50)

Due to the informal and often illegal nature of this distribution channel a much higher rate of counterfeits is seen in comparison to the legal supply chain. According to WHO data the rate for counterfeits bought in illegal Internet pharmacies is over 50 %. (25)

Different illegal supply chains have been detected in the past, however the origin of the counterfeit medicines often cannot be revealed.

The drugs are, as described above, often produced in China and are then transited through the Middle East and Europe. (42)

A few examples where the authorities have been able to investigate the lines of distribution shall be given below.

In 2007 a large counterfeit Viagra® operation could be busted by the British customs where the fake drugs have been brought to Britain, repackaged and then sold over the Internet to unknowing customers in 35 countries. (14)

Also in 2007 the MHRA had to recall different medicines batches due to detected counterfeits including batches of Zyprexa® and Plavix®. As source of these counterfeits China could be uncovered. They reached the EU through Mauritius und the UK packaged as French originals after transiting Luxembourg. (47)

Another criminal network imported the counterfeits from China to Naples where the Camorra took over and faked the legitimate packaging including the barcodes. From the port these frauds have then been transferred into the legal supply chain. (44)

In an effort to determine the geographic origin of counterfeited anti- malaria drugs Interpol and the WHO collected 391 samples of Artesunate, a commonly counterfeited medicine in South East Asia, bought in Cambodia, Vietnam, Laos and Myanmar were tested between 1999 and 2006. Around 50 % were proven to be counterfeit.

These counterfeits were further analysed and contained a certain mineral, calcite, certain pollen and insects and further impurities common only in a specific region in China. After handing over the evidence to the Chinese authorities these could arrest the vendors and identify the production site. (6) (39)

Even with the need to cover their steps and to act in secrecy the counterfeiters show a rising speed when introducing new counterfeits. While the first copies of Viagra® took 6 months to reach the markets, counterfeits nowadays can reach the markets at the same time as the new original. (47)

EU

The amount of counterfeits is on the rise also in well regulated and controlled markets like the EU. The DG TAXUD reported an increase of customs seizures of fake drugs of 380 % from 2005 to 2006. Counterfeit drug cases have risen to 2 % of all counterfeits seized by European customs.

Comparing the legitimate (27 cases reported to European Commission between 2001 and 2005) to the illegal supply chain (170 cases reported) it can be seen that illegally bought medicines show a much higher rate of counterfeits. However the legitimate supply chain is not completely secure in Europe either. (30)

The major source countries of counterfeits seized by European customs organisations include China, the United Arabian Emirates and India as shown in figure 5 below. (44)

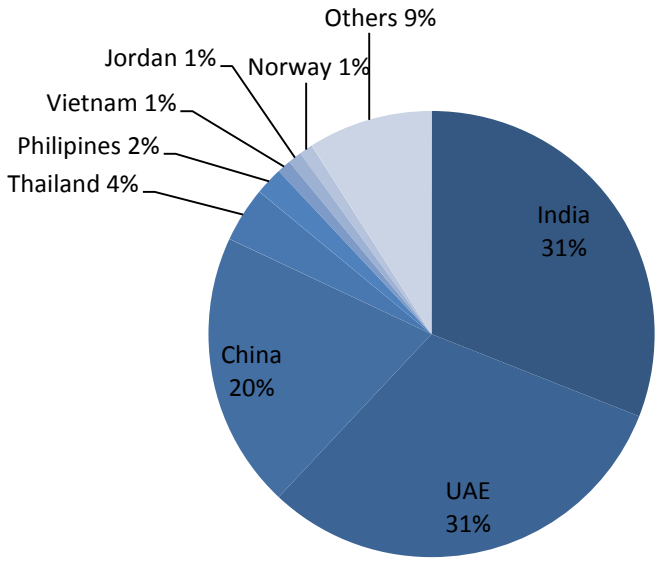


Figure 5: Source countries for counterfeits seized in the EU in 2006. Data derived from (44).

DE

As in other developed countries the Internet and mailing of medicines is a major source of counterfeits.
During a single campaign by the German customs 532 packages containing around 30,000 tablets from different pharmaceutical classes could be detected. (60)
The amount of seized counterfeits is rising in Germany as it is in other countries. Whereas drugs worth 2.5 million € had confiscated in 2006 by the German customs this sum more than tripled to 8.3 million € for 2007, where 2,400 cases of counterfeit medicines have been detected. (25) (32)
However most of the counterfeits do not reach the legal supply chain. Between 1996 and July 2009 only 40 cases have been reported to the German BKA where fake drugs were detected in the German legal supply chain. In most of the cases repackaged and illegally re-imported/parallel imported drugs have been found. (6) (47)

AT

Reports from Austria from 2007 show that India has been the main source, with a nearly 90 % share, of counterfeits detected by the Austrian customs (see figure 6).

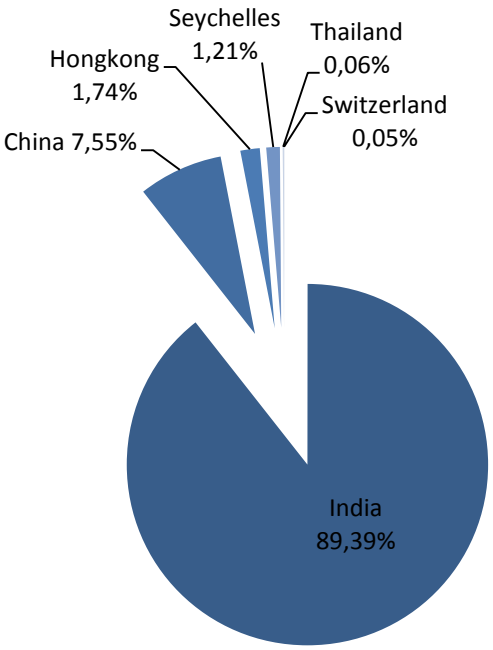


Figure 6: Source countries for counterfeits seized in the AT in 2006. Data derived from (24).

In terms of supply chains most counterfeits in Austria are bought in the Internet and delivered as small packages via mailing. (24)

UK

In Britain the legal supply chain seems to be as safe as in other developed countries. The MHRA reported 9 cases where counterfeit medicines reached the patients for 2004 to 2007. (14)
In 5 further incidences counterfeits reached the wholesaler level before being detected. (31)
The Internet is also a problem in UK when counterfeits are concerned highlighted by a British customs operation in 2007 detecting a plan to sell Viagra® and other drugs worth several million British Pounds. (14)

USA

The USA has to fight different problems concerning the distribution of counterfeit drugs.

The standard supply chains in the USA are rather safe. Three primary wholesalers provide 90 % of the prescription drugs to pharmacies and hospitals. The secondary wholesaler level seems to be more threatening for the legal supply chain as these have smaller quantities, higher turn-over and often more levels of seller and buyer included before the medicine reaches the patient. Besides these points raising the risk of introducing counterfeits in the supply chain unknowingly, some wholesalers may also try to raise their income by buying and selling fakes on intent. (17)

However as it is the case in other developed countries the main source for counterfeits in the USA is the Internet. In 2004 the U.S. Government Accountability Office published a study saying that 4 out of 21 samples bought from online pharmacies based outside of the USA or Canada were counterfeited medicines.

Due to the high drug prices in the USA some patients tend to buy their medicines from Canadian pharmacies, including Canadian online pharmacies. However at least a part of these are only fake websites covering the real location of the owner and the chances are high that these websites sell fakes. According to FDA estimations up to 85 % of ‘Canadian’ drugs originated in reality somewhere else, e.g. India or Costa Rica.

The FDA confirmed these speculations when testing drugs from several ‘Canadian’ pharmacies and detecting a great amount of counterfeits in 2005.

Genuine Canadian pharmacies also seem, to a lesser extent, to be a risk factor. The FDA detected multiple counterfeits in a shipment from one of the biggest USA selling Canadian Pharmacies in 2006, including fakes of Lipitor® and Celebrex® among others.

As the Canadian online pharmacies are not totally safe for the patients neither are the US ones as the DEA and the FBI uncovered in 2006 when two US Internet pharmacies where detected selling counterfeits to US patients. (14)

Latin America

Besides imported counterfeits locally produced ones are a major problem in Latin America.
These are not only produced for local consumption but also for export, as an incidence with counterfeit Lipitor® in Costa Rica showed, where tablets for the USA were produced by a counterfeiting network.
Furthermore, the existence of illegal pharmacies as well as the so called 'Pharmacias similares' where only generic drugs are sold make it easy to introduce counterfeits in the pharmaceutical market.
E.g. the Dominican Ministry of Health estimates that half of the country's pharmacies are not legal enterprises. Combined with the estimation that 10 % of all medicines imports are fakes, this gives a high chance to receive counterfeits as a patient. (14)

Russia

Locally produced counterfeits are also a problem for Russia where they make up to 70 % of the counterfeits market.
Russian plants producing legal drugs at day often run at night producing counterfeits. The fake drugs produced here are mainly for the internal market but also reach Europe or the US. (9)

Asia

Asia, besides being the source of the most counterfeit medicines produced in the world, also is a big market for the counterfeiters.
Especially the poorer countries in geographical proximity to India and China, lacking effective control of the pharmaceuticals in their supply chains, show a great share of fake drugs on their markets. For anti- malaria drugs the Chinese origin has been shown as described above. (14)

Africa

The origin for counterfeits in Africa is often India and China, consistent with the findings in other regions of the world.

Nigeria, in the past known to be a country with a rather high prevalence of counterfeits on its markets, even threatened to ban Indian drugs completely because of this fact. (23) That is hardly surprising given the fact that 31 companies from India, China and Pakistan have been banned from the Nigerian market between 2001 and 2005 alone for exporting counterfeit medicines to the country. (43)

However Africa does not only receive drugs but is also part of a transit route as investigations in Egypt laid open where a criminal network was found that delivered counterfeits to the Middle East region. (28) (58)

Consequences of counterfeit medicines

The consequences of counterfeit medicines can generally be divided into two main areas.
The first are economic effects for the pharmaceutical industry, health assurances and the national health systems and also the patients.
The second would be the more important direct health threats that the counterfeits can have for the patient and for medical treatment in general.
These areas are of course overlapping as health threats burdened on the patients also generate a major part of the economic effects for the other stakeholders.

Economic consequences for health systems and the society

Direct and indirect costs appear for the economic effect related to the patient.
The direct costs include everything concerning prevention, diagnosis and treatment of counterfeit related diseases, e.g. when patients need certain drugs to fight the effects caused by the counterfeit, if they need hospitalization or when their hospital stays are prolonged.
Indirect costs include the costs for the loss of productivity of the patients that fall ill, stay ill or even die because of counterfeits.
The countries affected by counterfeits can furthermore lose taxes and import/export duties as these are seldom paid by counterfeiters. (9)

Economic consequences for the pharmaceutical industry

The pharmaceutical sector also has to bear a considerable economic burden because of counterfeit medicines.
The companies are forced to investigate on the field of counterfeit medicines and take actions against them.
Recalls have to be done in the legal supply chain when counterfeits compromise certain batches of pharmaceuticals.
Confiscated counterfeits have to be destroyed, often at the costs of the holder of rights.
Higher costs lead to lower investments and less innovations, further lowering the economic potential of pharmaceutical companies. (9)

The brands and respectively the brand owning companies suffer from the damage of their reputation damaged by counterfeits which can lead to loss of market share and to the need for increased advertising efforts.
If counterfeits are detected in the legal supply chain, not only the pharmaceutical companies are less trusted, also retailers and pharmacies can lose market share and profits.

Economic consequences for the patients

As said before there are also economic effects for the patient. Apart from the effects of the over- or under dosed products, ineffective or even toxin-contaminated counterfeit, the enforcement of consumer rights is of course not at all secured with illegal pharmacies. Furthermore the Internet consumers risk their money due to pre-payment and the anonymity of the Internet. (24)
As the costs for the pharmaceutical industry rises with the prevalence of counterfeit medicines the patients will also have to pay higher prices for legal drugs. (54)
In addition, illness or prolonged illness is often associated with a loss of income for the patients.

EU

The costs for the EU health sector for the products that reach the legal supply chain have been estimated in a Commission Staff Working Document.
In this estimation, direct costs like prolonged hospitalisation and indirect cost, e.g. for recalls by the legitimate manufacturers or cost for the destruction of the falsified medicines, sum up to 950 million € per year for all stakeholders combined. (21)
Costs for counterfeits that reach the patient outside of the legal supply chain have to be added to this number.

Consequences for patient's health

The consequences for the patient's health due to the use of counterfeit medicines can be manifold.
Therapeutic failure, drug resistance and even death are possible as direct or indirect effects of their use.
The type of health effect that a counterfeit has depends on its type. As described in the definition chapter at the beginning there are many possibilities a counterfeit can be made.

Underdosing
Underdosing can lead to therapeutic failure with all related consequences and especially with anti-invectives also to microbial resistance against the API.

Overdosing
An overdose leads to an elevated risk for serious side effects.

Both under- and overdoses can also happen when the formulation of the drug is altered by the counterfeiters, e.g. the originator has a slow release formulation whereas the counterfeit is immediately released.

No API

If no API is used therapeutic failure will be the result and the medical condition of the patient might not improve or even get worse.

Switch to another API

If APIs are exchanged by counterfeiters not only the risks for under- and overdosed medicines apply, furthermore the 'new' API can have unexpected serious side effects.

Toxic substances

If toxic substances are included as fake APIs of course the toxic effects are the most apparent problem. Furthermore they will have no therapeutic effect.

Inferior Production of counterfeit production

Most counterfeits, even if they contain the correct amount of the correct API, are not produced according to pharmaceutical standards. Therefore all problems associated with insecure production like contamination with unwanted substances, microbial contaminations etc. are possible. (54)

A successful penetration of the legal supply chain also undermines the credibility of national health and enforcement authorities.

In the following sections some examples should be given for concrete health threats that happened in different parts of the world.

EU

Fatalities directly linked to counterfeit drugs are a rare event for the EU. However, as previously outlined, even the legal supply chain is breached from time to time and a certain risk for therapeutic failure remains even for EU patients.
An especially heavy case was the intentional contamination of Heparin with toxic Heparin-like substances that possibly led to the death of 81 patients. (21) Further examples are included in table 2 below.

Counterfeit medicine	**Country**	**Indication**	**Type of counterfeit**	**Health threat**
Heparin	BE, DE	Injectable anticoagulant	Counterfeit API, contaminated with toxic heparin-like substances	Possibly connected with 81 deaths and side effects in hundreds of patients due to allergic reactions.
Amoxicillin	BE	Antibiotic, used to treat bacterial infections caused by susceptible microorganisms	Underdosed with 75% level of API	Hundreds of thousands of packs. Therapeutic failure and resistance development possible.
Oseltamivir	BG	Antiviral drug for treatment of influenza	No API or severely underdosed.	Over 1000 packs identified and stopped by customs. Unknown quantity may have reached patients. Therapeutic failure and resistance development possible.

Counterfeit medicine	Country	Indication	Type of counterfeit	Health threat
Metamizole	BG	Antipyretic and analgesic for severe pain	No API.	Over 1000 packs reached patients. Therapeutic failure.
Indapamide	BG	Diuretic, antihypertensive medication	Formulation altered, wrongly declared to be slow release	2000 packs reached patients. Therapeutic failure.

Table 2: Examples of counterfeit cases and related health threats for the EU. Data derived from (21).

UK

As described before for the complete EU, UK also has seen a change in the medications counterfeited. 'Lifestyle' drugs like Viagra® or steroids are still copied but counterfeit lifesaving medicine against e.g. cancer find their way in the UP supply chain.

So far no fatalities have occurred, or have been detected. In Great Britain however the legal supply chain has been breached several times (see table 3). (36)

Counterfeit medicine	Country	Indication	Type of counterfeit	Health threat
Atorvastatin	UK	Statin, used for lowering blood cholesterol	Not published by MHRA	no immediate risk for patients (according to MHRA)
Clopidogrel	UK	Anti-platelet agent used to inhibit blood clots	Not published by MHRA	No assessment published by MHRA
Bicalutamide	UK	Non-steroid anti androgen, used for treatment of prostate cancer	Not published by MHRA	no immediate risk for patients (according to MHRA)

Table 3: Examples of counterfeit cases and related health threats for the UK. Data derived from (21) (35)

US

Similar to UK no fatalities have been attributed securely to counterfeits in the last decade. However as shown before the problems with counterfeits apply to the USA as they do to the EU. (17)

Canada

The first fatality in a developed country clearly connected to a counterfeited drug happened in Canada in 2007. Antidepressants and Paracetamol, purchased over the Internet, contaminated with toxic levels of aluminium, phosphorus, titanium, tin, strontium, arsenic and further metals led to the death of at least one patient (further examples of counterfeit cases in North America given in table 4). (17)

Counterfeit medicine	Country	Indication	Type of counterfeit	Health threat
Epoetin alfa	USA	stimulates erythropoiesis, used to treat anemia	Low pharmaceutical quality copy	Contained non-sterile tap water, infections in the bloodstream possible
Olanzapine	USA	drug used for schizophrenia and acute bipolar mania	Zyprexa bottles were emptied and the drug was replaced with white “aspirin” tablets.	Therapeutic failure
Somatropin	USA	growth hormone used in AIDS patients	No active ingredients	Therapeutic failure
Antidepressants and Paracetamol	CAN	-	Contaminated with toxic levels of aluminium, phosphorus, titanium, tin, strontium, arsenic and further metals	Intoxication

Table 4: Examples of counterfeit cases and related health threats for North America. Data derived from (17).

Middle and South America

Next to Parts of Asia and the sub-Saharan Africa, Middle and South America are especially targeted by counterfeit medicines producers.
A case leading to fatalities has been described for Argentina in 2004. A counterfeit of an iron preparation used to treat anaemia has been contaminated with toxin. After the death of a 22 year old woman the Argentinean Authorities tried to recall the batch in question. However due to the fragmented drug distribution system in Argentina the recall was only partially successful and a further death happened. (19)

Asia

For the WHO counterfeit and substandard medication is one of the serious problems in the greater Mekong sub region, including Vietnam, the Lao People's Democratic Republic, Cambodia, China, Myanmar, and Thailand. (61)
Beside the other counterfeits listed in the previous chapters about the prevalence and the nature of the counterfeits of the region, especially the malaria treatment is under attack by counterfeiters.
Malaria is one of the most dangerous diseases in the world, claiming one million lives a year and endangering 40 % of the total world population. Given the proper treatment chances of survival are high. (38) (39)
However due to the high demand anti- malaria drugs are a favourite target of counterfeiters and there are countless reports of e.g. fake Artenusate on the Asian markets. (14) (23) (28) (55)
As fake Artenusate often contains no or underdosed API, the counterfeits endanger malaria therapy options and control. They can lead to therapeutic failures and the emergence of resistances. (38) (54)

Another problem for the anti-malaria treatments in the regions of Asia and Africa affected by counterfeits are false positive reports of resistance of *Malaria falciparum* because of counterfeits containing no API. This may result in a loss of treatment options and further problems with the control of malaria, as drugs that would still be effective are not used because the malaria bug is thought to be resistant (further examples of counterfeit cases in Asia given in table 5). (55) (62)

Counterfeit medicine	**Country**	**Indication**	**Type of counterfeit**	**Health threat**
Unpublished	Singapore	Treatment of erectile dysfunction	API exchanged against glyburide (anti-diabetes drug)	150 people were admitted to hospital with hypoglycaemia, 4 deaths, 7 severely brain damaged (28)
Paracetamol	India, Bangladesh, Haiti, Nigeria	Analgesic	Contaminated with diethylene glycol	500 children died through renal failure (40)
Artenusate	SE Asia, several countries	Treatment of malaria	No API or underdosed	Therapeutic failure, emergence of microbial resistance, false resistance signals (28)

Table 5: Examples of counterfeit cases and related health threats for Asia.

Besides other Asian countries China, also one of the main producers of counterfeits, seems to suffer heavily under the burden of counterfeit medicines. In 2001 the Chinese authorities reported 192,000 deaths associated with counterfeits alone. (20) (23)

Africa

Africa has been traditionally one of the most important 'playgrounds' for medicines counterfeiters and therefore also suffered severely from this problem. In contrast to the low or nigh count of fatalities in the developed world many fatalities are reported for African countries.

As it is the case for some Asian countries malaria is a major issue also for sub-Saharan countries and the rising prevalence of fake anti-malaria drugs in Africa, especially fake Artenusate, is a major concern and health threat (further examples of counterfeit cases in North America given in table 6). (39) (55)

Counterfeit medicine	**Country**	**Indication**	**Type of counterfeit**	**Health threat**
Meningitis vaccine	Niger	Vaccination	unpublished	Led to 2,500 deaths, Ineffective vaccination, risk of meningitis infections, 60,000 patients inoculated (54) (63)
Paracetamol	India, Bangladesh, Haiti, Nigeria	Analgesic	Contaminated with diethylene glycol	500 children died through renal failure (40)

Table 6: Examples of counterfeit cases and related health threats for Africa.

Comparison

On a worldwide view it seems that there is no drug that is not counterfeited somewhere. And it seems that there is no place free of counterfeits.

However information from a variety of sources has been presented that allows a more differentiated look towards single countries and regions and objects the old WHO estimation for the worldwide prevalence of counterfeited drugs of 10%.
The new estimation indicating 1% prevalence of counterfeit drugs in the developed countries, 10% in the less developed with over 30% in a subset of these countries and 20% for the former Soviet states seems to be closer to truth. A special case and a problem especially for the more developed countries is the pharmaceutical trade over the Internet where illegal Internet pharmacies pose a considerable threat for consumers and a possible gateway for counterfeit and illegal drugs to enter the market.
When looking at the differences in the prevalence of fake drugs between regions and countries, it should not be forgotten that, especially for the less developed countries with an uneven distribution of governmental power, inside a single country there also could be significant differences between certain cities or cities and rural areas.
A worrying trend for the industrialised countries is the fact that these seem to be more and more targeted by drug counterfeiters. The numbers of seized goods as well as the counterfeit cases in different well developed countries have seen a fast rise leading to the assumption that the amount of counterfeits on their markets have risen considerably.
So the gap between developed and less developed states concerning the prevalence of counterfeit drugs on their markets remains a large one. The former have to take clear measures to keep the prevalence as low as it still is in their borders.

A clear difference cannot only be seen in terms of prevalence but also concerning the types of products counterfeited in certain regions. As stated above the counterfeit business is not restricted to certain drugs. Generics and innovative medicines are affected, cheap mass market drugs as well as high price items.

In the past the so called ‘lifestyle’ drugs’ including drugs for the treatment of erectile dysfunction, anabolic substances and medicines for weight loss made up the major part of counterfeited medicines in the developed countries. ‘Lifestyle’ drugs nowadays still account for the biggest share of counterfeits, especially when bought over the Internet, but other more crucial medicines, like medicines against cardio vascular diseases, psychiatric disorders and antibiotics, gain a higher prevalence.
In contrast the developing countries have always been plagued by fakes of essential medicines with a high share of antibiotics, anti-virals and anti- malaria drugs. However the whole range of pharmaceuticals has been forged in these countries.

Depending on the ‘quality’ of a counterfeit drug, it can either be made rather cheaply and easily in backyard facilities or be produced with more complexity in pharmaceutical factories. The latter is, for example, not unheard of in Russia where counterfeit drugs are produced sometimes alongside legal drugs.
The main production of counterfeits happens in Asia and to a strong degree in India and China, although counterfeit drug production happens from Russia to Latin America. These countries of origin for most of the counterfeited drugs seem to be the same for developed states as well as for the less developed ones. Some countries, e.g. Russia, also show a strong domestic counterfeit production, however most counterfeits around the world are an imported problem.
After production, often followed by shipping the counterfeit drugs through different free trade areas to disguise their origin, the products have to be introduced into the target markets which can either be the legal or the illegal supply chain.
The legal supply chain is a rather secure option for the patients in the industrialised countries. Only a low number of incidents are known where these well regulated markets have been breached, however it is also not unheard of. A trend is seen to target the legal supply chains in the developed countries and this trend is combined with higher quality fakes that are harder and harder to detect.
In the less regulated and controlled markets the legal supply chain can be a problem when counterfeit drugs are concerned und these are not uncommon e.g. in Africa or parts of Asia.

A major problem and source for counterfeit medicines are illegal sources for pharmaceuticals in less developed as well as in developed countries. Whereas in the former often street vendors and illegal pharmacies are a counterfeit source, the Internet and illegal Internet pharmacies are these sources in the more developed countries.

Counterfeit drugs can lead to several consequences. These can be either of economical nature or concern the health and well-being of patients. The former is effecting all stakeholders from pharmaceutical industry to the patients whereas the second effects the national health systems and of course mostly and most prominently the patients.
Pharmaceutical companies lose money due to counterfeits when their products are forged. This holds true for the developed states where most of the innovative products originate as well as for some of the less developed, e.g. China or India, where many generic products are made. On the level of national health systems and patient's level however the effects for the less developed countries are much more severe as these are less able to cope with the problems caused by counterfeit drugs.
The consequences for patient health are seldom severe in developed countries and only single cases are known where counterfeit medicines led to the death of patients, with the exemption of the Heparin case that possibly led to the death of 81 patients. Due to the rather low amount of counterfeits in the supply chain and due the problems to detect the effects of counterfeits drugs, many cases may not be known though.
In less developed countries a higher prevalence of counterfeits exits as described above, furthermore the fake drugs mimic crucial medicines more often and are of an inferior quality. This leads to a higher amount of fatalities attributed to counterfeit drugs with single incidents affecting and sometime killing thousands of patients. Even if the effect is not the death of the patient, the health consequences are often more severe because no correct medical treatment or medicine alternatives, e.g. in the case of failing malaria treatment, may be available.

Counterfeit drugs exist due to a variety of reasons. The main reasons in less developed countries are insufficient or missing regulations, insufficient or missing authorities, insufficient law enforcement and insufficient penalties. With weak, unwilling or corrupt governments or institutions these reasons lead to the high amount of counterfeits seen on the market of these countries.

While insufficient penalties also can be found to a lesser degree in the more developed countries, other reasons completely apply for both.

A common problem is the rising quality of counterfeit drugs making them harder to detect. Especially labelling and packaging are close to the originals including security details like holograms e.g. for certain anti- malaria drugs in South East Asia or in a Neupogen® case in the US.

Information about counterfeits can be another problem when the different stakeholders do not cooperate as close as they must to combat counterfeit drugs. A lack of information can also lead to a lack of awareness by health professionals and patients, a problem seen in developed and less developed states.

As the trade routes for APIs and finished drug forms become more and more complex they also become harder and harder to control. The problem holds true for developed and less developed states, however with the later not having the option the former have, e.g. in terms of control laboratory or good functioning customs services, the less developed states are effected stronger by this problem.

High prices and a disparity between supply and demand are also a problem of both worlds. In developed states innovative medicines may be too expensive for a part of the population and alternatives from dubious Internet sources may become more interesting. Furthermore not all medicines are available on the legal prescription market and patients may be willing, to buy from outside the legal supply chain with a manifold higher risk of receiving counterfeited drugs.

In some less developed countries on the other hand even relatively low priced generics may not be low priced enough for the average patient, or even simply not available everywhere. Street vendors or illegal pharmacies selling cheaper loose pills or single blisters may then seem to be an interesting option.

Outlook

Despite all differences described above, the threat of counterfeit medicines exists for both, the industrialized countries and the developing countries.

The majority of the developing countries still show a significantly higher prevalence and a higher share of crucial medicines counterfeited. However more and more crucial medicines are faked in the industrialized countries as well and the legal supply chains of these countries receive more pressure every year.

Counterfeit medicines threaten live and health as well as economical points and the fight against counterfeit drugs should be a major priority of all stakeholders involved.

In developing countries the founding of new or the strengthening of existing drug regulatory authorities and medicines control organs seems most important, whereas industrialized countries should take action to keep the supply chains secure. In general, the information of the public should be improved.

Although it might not be feasible to suppress counterfeit medicines completely it should be possible and it should be the aim, with the right will and the right measures, to lower the rate of counterfeits in the developing countries considerably and to keep the high standard in the industrialized ones.

Summary

Counterfeit drugs have a long history. As early as 400 B.C. there have been warnings of their presence and Dioscorides, a Greek physician, pharmacologist and botanist living from 40 – 90 AD, wrote in his 'Materia Medica' about the detection of counterfeit drugs. The threat of counterfeit medicines therefore hardly is a new one and it persisted through the ages. The 'modern' issue of counterfeit medicine emerged in the 1980s when more and more member states of the WHO reported counterfeit medicines. It was first brought to a greater attention on an international conference on the rational use of drugs in Nairobi 1985.

The WHO defines counterfeit medicines as a subset of substandard medicines which are deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeit drugs can contain the wrong ingredients, not enough or no API at all. Counterfeit of Packaging and/or PIL are also commonly seen.

Besides the risk of not receiving the correct medicines and therefore not the correct treatment for their diseases, patients taking counterfeit drugs also have the risk that the wrong ingredients these drugs often consist of are harmful themselves. These harmful substances included in counterfeit drugs in the past include for example diethylene glycol in cough syrup.

Both branded and generic drugs are counterfeited, however patent and high priced medication is more likely to be counterfeited.

Counterfeit medicines are present in industrialized and developing countries. The extent of the problem and several other factors concerning the counterfeited drugs however differ significantly between industrialized and developing countries. Of course the extent depends on the drug regulation control and enforcement and on the quality and the prices in the legal supply chain. In most industrialized countries like the USA, Japan or the members of the EU the extent of counterfeit drugs is below 1% share of the total medicines market value. An exemption is the former Soviet Union where up to 20% of the market may consist of counterfeit drugs. In contrast in great parts of Africa, Asia, Parts of Latin America between 10 and 30% of the available medicines are fakes.

Not only the extent of the problem differs between wealthier and poorer countries but also the types of medicines counterfeited. In industrialized countries often lifestyle medicines like slimming pills and anabolic drugs are faked. The best known symbol of counterfeit drugs is of course the widely known medicine against erectile dysfunction 'Viagra®'. In developing countries however often more crucial medicines are faked. This includes antibiotics and drugs against very prevalent diseases like malaria, HIV/AIDS or tuberculosis.

The aim of this master thesis is to present a current, compact and accurate view of the problem of counterfeit drugs on a worldwide basis. It should especially address and list the differences of the problem in industrialized and developing countries to be able to make a comparison. It should furthermore address the reasons of these differences.

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

(Sebastian Strobl)