

Patient Safety Problems Related to Drug Counterfeiting

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- From the year 1640, that the Peruvian Bark was first imported into Spain, its reputation increased till the old unpeeled trees becoming scarce, the inhabitants of Loxa, mixed other Barks with it, which being detected, it fell into discredit, that, in the year 1690, several chests of it lay in the warehouses at Piura, and nobody to purchase it. From this circumstance, and from the insignificant doses in which it was administered, it disappointed the public expectation so much, as to be generally discarded, till Tabor, an adventurous English practitioner, by giving more adequate doses of the genuine drug, revived its reputation; when its fame spread so rapidly, that the Spanish merchants, at length, found it difficult to supply the demand of their customers for full grown Bark, and therefore partly through necessity, and partly through political economy, substituted the *small* Bark with which they have long furnished the European markets
 - Hence, 17th Century

Outline

- Counterfeiting
 - Definitions
 - History
 - Extent of the Problem
 - National Examples
- Patient Safety and Counterfeit
- Preventing Counterfeiting
- Conclusion

Counterfeiting

Patient Safety Problems Related to Drug
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Alert over counterfeit high street medicines



Definition

Counterfeit Medicines

- A counterfeit medicine is one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging
 - *1st International meeting on counterfeit drugs, 1-3 April 1992, Geneva, Switzerland. Organised by WHO and IFPMA*
- *Definition subject to several discussions and debates and may change soon*

Definition

Substandard Medicines

- Substandard drugs are genuine drug products that do not meet quality specifications set for them. If a drug, upon laboratory testing in accordance with the specifications it claims to comply with, fails to meet the specifications, then it is classified as a substandard drug
 - WHO, 2006

Counterfeit medicines vs. Substandard medicines

Substandard medicines

- Known manufacturers
- Known manufacturing process
- Problems could be due to legitimate and honest errors
- No intent to mislead

Counterfeit Medicines

- Unknown origin
- Main intent is to mislead or deceive for financial gain
- Problems with the product integrity cannot be justified due to the intent and motivation of the manufacturers/suppliers

History

General

- 1st Century AD
 - Dioscorides
 - Warned of the dangers of adulterated drugs and advised on their detection
- Others
 - Adulterated *Valeriana officianalis* (used for treating cholera)
- 17th Century
 - Adulteration of Peruvian Cinchona bark (used to treat malaria)
- 19th Century
 - Adulteration of quinine and introduction of guides on detection of counterfeits
 - *Lancet* 1848, Vol. 1:104
 - *Heath, Food and Drug Law Journal* 2004; Vol. 59: 169-200

History

World Health Organisation

- 1951
 - Executive Board Resolution EB7.R79 requesting the Director-General to consider the advantages of more uniform methods for the control of drugs in countries in the interest of health and international commerce
- 1985
 - First international discussion on counterfeits at the Conference of Experts on the Rational Use of Drugs in Nairobi Kenya
 - Meeting recommended that “WHO should identify the feasibility on setting up a clearing house to collect data and to inform governments about the nature and the extent of counterfeiting

History

World Health Organisation

- 1988
 - World Health Assembly resolution WHA41.16
 - Requested Director-General of WHO to initiate programmes for the prevention and detection of the export, import and smuggling of falsely labelled, counterfeited or substandard pharmaceutical preparations
- 1992
 - First International workshop on counterfeit drugs organised by WHO and IFPMA
 - Agreed on a definition for “counterfeit medicines”

History

World Health Organisation

- 1994
 - World Health Assembly resolution WHA47.13
 - Requested the Director General of WHO to assist member states in combating the use of counterfeit medicines
- 2006
 - WHO's launch of the International Medicinal Products Anti-Counterfeiting Taskforce (IMPACT)
 - Coordinates WHO work against counterfeit medicines

Types of Counterfeit Medicines

- Products which do not contain any of the specified active ingredients despite such declarations on the label
- Products which contain active ingredients other than those specified on their labels
- Products which contain the correct strength of the specified active ingredients but whose source is different from the one declared
- Products which contain the specified active ingredients but in strengths different from those declared; they may also contain different or different quantities of impurities
- Products with fake packaging

Types of Medicines Counterfeited

- Branded products
- Generic Products
- Medicines for life-threatening conditions
- Medicines for chronic conditions
- Medicines for mild conditions
- Herbal medicines

- Main medicines counterfeited in developing countries are anti-infectives whilst the main medicines counterfeited in developed countries are those for chronic conditions or lifestyle diseases
- Motivation for counterfeiting
 - Profit

It affects products of all kinds



**Expensive,
prescription**



Inexpensive, OTC



Inexpensive, generic



“Counterfeit medicines are a threat to our communities and must be stopped. The problem is not isolated to a handful of countries; it is present everywhere and it is gaining momentum. It is not a problem of one person, it is the problem of all people. It is not a problem of one country, it is a problem of all nations”

- *Zucker H. 2006 (speech at IFPMA)*

Where do we find counterfeit medicines?

- Everywhere
 - Counterfeits are estimated to be up to 15% of the global trade in pharmaceuticals generating US\$75 billion per annum in 2010 (Nelson et al., 96 Trademark Report 1068. 2006)
- EXTENT of the problem varies from country to country and between urban and rural areas within the same country
- Less than 1% of products in developed countries are counterfeits
- Figure for developing countries difficult to obtain but can be in excess of 50% for some products in some countries
- “many developing countries of Africa, parts of Asia and parts of Latin America have areas where >30% of the medicines on sale can be counterfeit. Other developing markets however, have <10%
 - IMPACT 2006

Face to face with counterfeits: examples from countries

Nigeria

- 1997
 - 48% of anti-infectives contained no active ingredient. All proguanil tablets, co-trimoxazole tables and quinine injections and syrups passed but no pyrazinamide or isoniazid tablets, chloroquine syrups or metronidazole suspensions passed (Shakoor et al., TMIH, 1997; 2:839-45).
- 2001 research by Nigerian Institute of Pharmaceutical Research
 - 80% of drugs distributed in major pharmacies in Lagos, Nigeria were counterfeit
 - Regulatory interventions have led to a reduction by about 90% by 2006
- 2001
 - Lancet study (Taylor et al., Lancet 2001, June 16; 357 (9272): 1933-6
 - 48% of drugs sampled did not comply with pharmacopoeia limits. Some preparations contained no active ingredient

Sierra Leone

- Counterfeit antibiotics
- Counterfeit anti-diabetics
- Counterfeit anti-malarials
- Toothpastes with high amounts of mercury
- National Drug Regulatory Agency now has billboards all over the country cautioning the population on the harmful effects of counterfeit medicines

Ghana

- Counterfeit antimalarials (2010 – Coartem)
- Nearly 50% of samples of main anti-malarials sampled failed (QAMSA study)
 - Failure rate high as 80% for some compounds
- Substandard anti-diabetics found
- Diazepam injection with less than 20% active ingredient found
- Vit K3 (instead of Vit K1) injection also detected

UK

- 2006: Counterfeit Lipitor detected in supply chain; lacked sufficient active ingredients
- 2007: 10 reported cases of counterfeit condoms, packaged to a high standard but deficient in terms of quality and performance
- 2007: Counterfeit Zyprexa found in supply chain; lacked sufficient active ingredient

China

- 2001: Government closes down 1300 factories and investigated 480000 drug counterfeiting cases involving drugs valued at US\$57 million (see Newton et al., 2006; Lancet Infect. Dis. 6:602-13)
- 2009: Anti-diabetic traditional medicine found to contain six times the normal dose of glibenclamide
- 2009: Quality problems with heparin injections

USA

- Investigations by the US FDA into drug fraud increased four fold from 2003 to 2010
- FDA has seen an 800% increase in the number of new counterfeit cases between 2000 and 2006
- 2007: Counterfeit Xenical containing no active ingredient

Others

- Tanzania
 - 2009: Metakelfin (anti-malarial) with lower than expected active ingredients)
- Thailand
 - Viagra and Cialis found with country of origin unknown
- Mauritius
 - 1999: Substandard gentamicin eye drops contaminated with *Pseudomonas aeruginosa* leading to an outbreak of postoperative eye infections
- Pakistan
 - 2009: 15.62% of ceftriaxone injection found to be out of specification though all were “registered” products

Counterfeit Diabetes Products

Cheng, J. Diab. Sci. And Tech. 3(6):1516-1520

- Counterfeit anti-diabetics
- Counterfeit insulin leading to death
- Counterfeit glucose test strips
- 2006: One million counterfeit OneTouch test strips in 35 states in the US
 - Manufactured in China and giving incorrect readings
 - Chinese businessman responsible apprehended and sentenced in 2007

Counterfeit PDE5is – I

Jackson et al., 2010; Int. J. Clin. Pract 64(4):497-504

- Medicines for erectile dysfunction (ED) represent one of the most widely counterfeited class of drugs currently
- Sildenafil (Viagra); Tadalafil (Cialis) and Vardenafil (Levitra) are the most likely to be counterfeited
 - Price is high; Patients often embarrassed to seek treatment for ED; Internet sales very high

Counterfeit PDE5is - II

- 2004-2008
 - 35.8 million counterfeit sildenafil tablets sized in Europe
 - In 2004, 10.6 million sildenafil tablets sized = seven times the number of all other counterfeited Pfizer products combined
 - In 2006, 2.5 million counterfeit sildenafil tablets seized in the UE accounting for 96% of the counterfeit Pfizer products seized

Counterfeit PDE5is - III

- Content of the counterfeited PDE5is
 - Inconsistent API ranging from 0% to 200% active pharmaceutical ingredients
 - Only 10.1% of samples labelled “Viagra 100mg” were within 10% of advertised strength
 - Counterfeit Viagra from Hungary contained amphetamine
 - Counterfeit Viagra in the UK contained 30% API plus talcum powder, commercial grade paints, caffeine, lactose
 - Paracetamol and metronizazole have been found in counterfeit Viagra

Counterfeit PDE5is - IV

- Content of the counterfeited PDE5is
 - Dutch National Institute for Public Health and Environment analysed 370 samples of illegal sold Viagra
 - Only 10 were genuine
 - Viagra often present in low amounts in addition to other compounds such as amphetamine, tadalafil, yohimbine, gamma-amino butyric acid, caffeine, L-arginine, indigotin and quinine
 - US National Association of State Board of Pharmacy examined Cialis purchased from 13 suspicious websites
 - Content varied from zero to excessive amounts
 - None met the company's US standards

Factors that *promote* counterfeiting

- Main cause of counterfeiting is profit
- However, the distribution of counterfeit medicines is facilitated by several factors
 - Weak regulatory systems
 - Weak supply chain systems
 - High cost of medicines especially when patients pay out of pocket
 - Erratic availability of essential medicines
 - Existence of non-formal outlets for sale of medicines
 - Proliferation of internet sales

Patient Safety Problems Relating to Counterfeiting (and substandard drugs)

The tragedy of diethylene glycol

Alkathani et al Arc Dis Child 2010, 95:1062-1064

- DEG poisoning due to counterfeit and substandard products well known
- However, they still occur
 - Classic example of preventable problems not being prevented despite nearly 100 years of experience of the problems
 - 1st reported episode 1938
 - Problem still ongoing.....

DEG Deaths and Problems

Year	Country	Deaths in Children	Overall Deaths	Overall cases
1937	USA	34	105	353
1969	South Africa	7	7	14
1987	Spain	0	5	5
1990	Nigeria	47	47	47
1990	Bangladesh	51	236	339
2008	China	0	12	15

Patient Safety Problems - I

- Treatment failure
 - Seen when counterfeit anti-infectives with low amounts of active ingredients are dispensed
 - Seen with anti-infectives, especially in developing countries
 - Main classes of anti-infectives counterfeited are
 - Anti-malarials
 - Anti-retrovirals
 - Anti-tuberculosis medicines
 - Antibiotics
 - References
 - Newton; PLoS 2006 Medicine 2006; 3: e197 Newton et al., PLoS Medicine 2008; 5:e32; Laing, Int. J. Tuberc. Lung Dis. 2004; 8: 1043-1044; Newton et al., Lancet Infect. Dis 2006; 6: 602-13

Patient Safety Problems II

- Treatment failure
 - Hyperglycaemia due to the use of counterfeit insulin
 - Failure of blood sugar control due to the use of counterfeit oral hypoglycaemics
 - ED problems including priapism due to the use of counterfeit PDE5is
 - Failure of diazepam injection to manage convulsion in children and to sedate adults
 - Failure

Patient Safety Problems - III

- Adverse reaction by patients to the “additives and substitute products”
 - Allergic reactions when sulphonamides are used to replace artesunate in anti-malarials
 - Reactions to amphetamines used to replace PDE5is
 - Disulfiram-like reaction when metronidazole is used to substitute sildenafil
 - Potential overdose of paracetamol when it is used to substitute PDE5is
 - Toxic reactions when aminoglycosides and other antibiotics are used as substitutes in antimalarials or more expensive antibiotics

Patient Safety Problems - IV

- Worsening of disease and possible death due to progression of disease as sub-optimal doses of medicines are unable to treat the conditions
- This will be commonly seen in conditions like
 - Malaria
 - Upper respiratory tract infections
 - Diabetes
 - Asthma
 - Tuberculosis

Patient Safety Problems - V

- Reactions to the following which have all been detected in counterfeit medicines
 - Clomifene
 - Amphetamine
 - Chloramphenicol
 - Dipyrrone
 - Tetracycline
 - Fluoxetine

Patient Safety Problems - VI

- Potential development of resistance
 - Artemisinin-combination therapies
 - Newton et al., PLoS Medicine 2008; 5: e32
 - Anti-tuberculosis drugs
 - Laserson et al., Int. J. Tuberc Lung Dis. 2001; 5: 448-54;
Laing et al., Int. J. Tuberc. Lung Dis. 2004; 8: 1043-44
 - Anti-retrovirals
 - Nsimba, East Afr. J. Publ. Health 2008; 5(3): 205-210

Patient Safety Problems - VII

- Outbreak of hypoglycaemia in patients using counterfeit sexual enhancement drugs due to contamination of counterfeit tadalafil with glyburide, a powerful drug used to treat diabetes
 - Kao et al., N Engl. J. Med. 2009; 360: 734-6
- Use of counterfeit oral contraceptives can lead to unwanted pregnancies and its attendant problems
 - Unknown exposure of foetus to medicines
 - Abortion which may be unsafe

Patient Safety Problems - VIII

- Deaths
 - Several reported and unreported cases
 - Often difficult to tease out unless on large scale
 - Treatment failure and death often raise the first signal of a problem with counterfeit medicines
 - 192000 deaths in China in 2001 due to “bogus” drugs (Fackler M., San Francisco Examiner, July 29, 2002)
 - Two women in Argentina died after being given injections of counterfeit iron preparations (IMPACT brochure)

Other Patient Safety Problems -IX

- Loss of money and loss of productivity
- Long stay in hospitals and possible change in diagnosis leading to exposure to other medications which may have their own toxicities
- Resort to other forms of treatment including alternative remedies which may be untested
- Disease progression and complication
- Loss of trust in healthcare system

PV and Anti-Counterfeit

- **PHARMACOVIGILANCE**

- Protection of patients
- Avoiding harm
- Collection and sharing of information
- Investigation and Mitigation
- Information provision and communication with patients
- Risk Management

- **ANTI-COUNTERFEITING**

- Protection of patients
- Protection of brands
- Avoiding harm
- Collection of information (systematic sharing?)
- Intelligence gathering and sharing
- Information provision and communication with patients
- Risk Management?

PV and Anti-Counterfeiting

- Spontaneous reporting system (and active studies) may give first signal of a drug use problem
 - Collection of unusually high numbers of mild adverse events
 - Clusters of adverse events
 - Reporting of adverse events to “old” drugs which have had no reports
- Cohort and other active studies
 - Adverse events associated with change of manufacturers or brands

Medicines of Interest

- Medicines for priority conditions
 - HIV/AIDS, TB, Malaria
- Medicines with high value
- Medicines with high volume of sale
 - Antibiotics, hormones, analgesics, steroids, antihistamines, medicines for lifestyle diseases

Strategies to Counteract Counterfeiting - I

- Multi-stakeholder approach needed for any lasting strategy to counteract counterfeiting
- The following stakeholders are particularly important
 - The Pharmaceutical Industry
 - Importers, Wholesalers and Retailers
 - Health Professionals
 - Consumers and The media
 - National governments, regulators, law enforcement agencies

Strategies to Counteract Counterfeiting - II

- The following actions are important to prevent and counteract counterfeiting
 - Strengthening political will and commitment
 - Promulgating strong and appropriate legislation
 - Establishing and strengthening of national drug regulatory agencies
 - Police and Custom Action
 - Enforcement of laws against counterfeiting

Strategies to Counteract Counterfeiting - III

- Actions to counteract counterfeiting (continued)
 - Increased public awareness
 - Transparency
 - Access to affordable good quality medicines
 - National, regional and international collaboration and cooperation and sharing of information
 - Research

Thank You

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