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ABSTRACT
Spread of spurious/counterfeit/substandard drugs is a modern day menace which has been recognised internationally, especially so in developing countries. The problem assumes added significance in view of rapid globalisation. The market of spurious and counterfeit drugs is a well-organised, white collar crime. Poverty, high cost of medicines, lack of an official supply chain, legislative lacunae, easy accessibility to computerised printing technology, ineffective law enforcement machinery, and light penalties provide the counterfeiters with an enormous economic incentive without much risk. The consequences of the use of such medicines may vary from therapeutic failure to the occurrence of serious adverse events and even death. Proper drug quality monitoring, enforcement of laws and legislation, an effective and efficient regulatory environment, and awareness and vigilance on part of all stakeholders can help tackle this problem.

There has been wide ranging international concern about the menace of spurious/counterfeit/substandard drugs. The published estimates about the global prevalence of counterfeit drugs range from 1–50%. This problem is, however, much more severe in the developing countries; the World Health Organization estimates that about 25% of the medicines consumed in developing countries are believed to be counterfeit. The vast majority of counterfeit medicines are currently thought to be produced in China, India and Russia, although significant numbers of illegal factories have also been reported in Nigeria and the Philippines. This article highlights the salient features of the spurious and counterfeit drug industry in relation to developing countries, with special reference to the laws and conditions in India.

SPURIOUS AND COUNTERFEIT DRUGS

In India, The Drug and Cosmetic Act 1940 and Rules 1945, a central piece of legislation regulating the manufacture, sale, and quality of drugs and formulations, provides a definition of "spurious drugs" under section 17-B.4

3. If the label or container bears the name of an individual or company purporting to be manufacturer of the drug, which individual or company is fictitious or does not exist; or
4. It has been substituted wholly or in part by another drug or substance; or
5. If it purports to be the product of manufacturer of whom it is not truly a product.

According to WHO: “Counterfeit drug is one which is deliberately and fraudulently mislabelled with respect to its identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit medicines may include products with the correct ingredients but fake packaging, with the wrong ingredients, without active ingredients or with insufficient active ingredients”. In other cases, drugs which have been rejected by regulators or manufacturers may be sold in markets and should be considered counterfeit. The same holds true for drugs which have expired and have been relabelled with a fake later expiry date.

Indian drugs laws, however, do not define or make note of the term “counterfeit drugs” throughout the statute, although there is an immediate need to incorporate this term under its purview. Bearing in mind the fact that India has emerged as a bulk manufacturer and exporter of drugs and pharmaceuticals, the quality of drugs manufactured in India and its regulatory mechanisms are of paramount importance, not only for India but also for the whole world.

In developing countries, drugs used to treat life threatening conditions such as malaria, tuberculosis, HIV/AIDS, etc, are generally counterfeited. In developed countries, counterfeiters generally target newer and costly drugs like hormones, steroids, psychiatric medicines, anticancer drugs, etc. During the year 1999–2000, up to 35% of artesunate (a life saving antimalarial drug), labelled as being manufactured by Gulin Pharma, People’s Republic of China, and bought in pharmacies and shops in Burma, Cambodia, Vietnam and on the Thai/Burma border, contained no detectable artesunate.

Spurious and counterfeit drugs are not synonymous with each other and a clear line of demarcation needs to be drawn between the two (table I).

MAGNITUDE OF THE PROBLEM

The problem of spurious and counterfeit drugs has been escalating the world over in spite of tough provisions provided in drug laws in most countries to counter this problem. In India, the death penalty has been discussed as a penal action in
case of conviction in a spurious drug case.10 Fake drugs are estimated to represent 13–30% of the pharmaceutical market in India.11–13 A survey suggested that in India’s major cities one in every five medicines sold was fake.9 According to another report released by the European Commission, 75% of global cases of counterfeit medicines originated from India.14 India is also the major exporter of counterfeit drugs to the least developed countries such as Nigeria, including anti-HIV drugs.15

The human right to a standard of living adequate for health and well-being is an important right that is recognised in the International Bill of Human Rights.16 Although the Indian Constitution does not explicitly mention health or health care as a fundamental right, the legal right to health is based on right to life and liberty (article 21 in part III of the Constitution of India). This right to health has to include the right to access quality medicines to be of any value; thus, the state is duty bound to provide quality medicines to its people.

FACTORS ENCOURAGING GROWTH OF SPURIOUS AND COUNTERFEIT DRUG MARKET

Poverty, high cost of medicines, lack of an official supply chain, legislative lacunae, inadequate/weak drug control infrastructure, and light penalties give the counterfeiters an economic incentive without comparable risk. This trade is a well organised, white collar crime. Highly remunerative trade, availability/accessibility of advanced printing technology, sickness in small scale industry, lack of coordination between various law enforcing agencies, inadequate testing facilities, and poor infrastructure are some of the factors responsible for the growth of this market of spurious and counterfeit drugs.1 5 In India the offences related to spurious drugs have remained undecided for years because of tardy trial procedures, to the advantage of the culprits. The accused are released on bail as the offences under the Indian law are bailable.17

Production of such drugs does not require large infrastructure or facilities. Moreover, the investment required is not large and the technology is accessible. This can be brought about in ordinary houses, backyards and small cottage industries.1 5 Huge quantities of spurious/counterfeit drugs were recently detected/confiscated by the drugs regulators from residential premises in a suburban area of Kalka (Haryana), wherein the packing and batch printing of some leading brands of drugs—for example, cefuroxime tablets (Ceftum, GSK), diclofenac tablets (Voveran SR, Novartis) and atorvastatin tablets (Atorva, Cadila)—was being carried out using manual techniques. The manufacturing operations were being done so secretly that even the neighbours were totally unaware of the activity.15

When prices of medicines are high and price differentials exist between identical products, there is greater incentive for the consumer to seek medicines outside the normal supply system. Easy access to counterfeit drugs, especially in the tropics in large open air markets alongside fruit and vegetables, makes this a flourishing business.17 Often the patients here obtain medicines from untrained vendors without prescription, in inadequate courses, and without information.8 Internet based sales of pharmaceuticals remain a major source of counterfeit medicines, threatening those who look forward to cheaper or unauthorised treatments.1 5 More than 50% of the products purchased from internet sites that conceal the actual physical address are counterfeit.9

Corruption is an integral factor in the propagation of this evil. Staff members of one drug regulatory authority allegedly accepted bribes to pass spurious drugs for sale.16

Another important factor to be considered in the spread of counterfeit drugs is smuggling and illegal cross border trade of these drugs. Counterfeiters employ all types of subterfuge for illegal cross border trade of these drugs, including setting up of fake front companies and procuring fake certificates and documents for exporting and importing pharmaceutical ingredients as well as machinery.17

MANUFACTURE OF SPURIOUS AND COUNTERFEIT DRUGS

The two important domains which the manufacturers of spurious drugs manipulate are:

► raw material which includes both active ingredients as well as inactive ingredients (excipients)
► packing material which includes labels, printed cartons/strips, holograms etc.

Raw material (active ingredients)

Raw materials are the starting materials for the manufacture of a medicinal product. Every drug product must have the labelled quantity of the active ingredient/raw material as per the statutory requirement. Manipulations in the active raw materials during the manufacture of drug products may lead to the genesis of a spurious drug product. Substitution of API (active pharmaceutical ingredient) with inert material (for example, making a tablet of alprazolam with simple calcium carbonate instead of the legitimate raw material); the purchase of raw material of short expiry or unknown expiry or unlabelled raw material or purchase from an unauthorised/doubtful source so as to reduce the manufacturing cost; and substitution of the API with a cheaper API which has a very similar therapeutic action (for example, cefotaxime with ampicillin; analgin with paracetamol) may all lead to the generation of spurious/counterfeit drug products.

Another aspect to be considered is the stability of the sensitive raw material. Most of the drugs require particular storage conditions; if they are not stored in these mandatory storage conditions, they tend to lose their potency. Drugs such as ampicillin, gentamycin, oxytocin, insulin, vitamins, etc, require storage at controlled temperatures and specified humidity throughout their process of manufacture and afterwards. Usually no strict compliances are made to their storage conditions by the manufacturers/traders in developing countries, affecting the quality of the product to the detriment of the end users—the patients.

Table 1 Distinction between spurious and counterfeit drugs

<table>
<thead>
<tr>
<th>Spurious drugs</th>
<th>Counterfeit drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The drug product/formulation is without any active ingredient/salt</td>
<td>1. The drug product/formulation contains labelled drug</td>
</tr>
<tr>
<td>2. Sample will fail when tested in the laboratory</td>
<td>2. Sample may pass when tested in the laboratory</td>
</tr>
<tr>
<td>3. It may or may not resemble in packing, design, look, etc with popular original brand</td>
<td>3. It will resemble in packing, design, look with popular brand. The batch number, manufacturing date, expiry date, labels on the product may be from the original pack. Even the physician/pharmacist may not be able to detect it</td>
</tr>
<tr>
<td>4. Injurious to health; may cause problems even death of the patient</td>
<td>4. May not be injurious to health</td>
</tr>
<tr>
<td>5. Normally the medicines are sold without bill</td>
<td>5. Medicines may be sold on valid invoices by licensed chemists</td>
</tr>
<tr>
<td>6. There is criminal intent behind producing and supplying these drugs</td>
<td>6. Criminal intent may or may not be there</td>
</tr>
</tbody>
</table>
Raw material (inactive ingredients/excipients)
If the swallowed tablet passes through the patient and out with the stool, without disintegrating in the stomach, it is useless to the patient even if it contains the required quantity of therapeutically active ingredient. The solvent (excipient) added to dissolve the drug powder paracetamol may prove fatal if it is not pure. Herein lies the importance of these hidden materials, which do not contribute to the therapeutic efficacy, but may result in a heavy cost if their quality is not ensured or is compromised by the manufacturer. Such materials are known as excipients, fillers, and vehicles.

Using poor quality solvents/vehicle—for example, purified water, glycerine, propylene glycol, etc—in the formulation may lead to a spurious/adulterated/sub-standard product. Poor microbiological quality of water in the manufacture of large volume parenterals can be fatal when given intravenously. Use of inadequate/incompatible preservative or vehicle, either by oversight or deliberately or as part of cost reduction exercise, may lead to a substandard drug product.

Packing materials (labels/cartons/strip, etc)
Because of advances in computerised printing technology, the drug producers have been able to achieve excellent results with both the printing and packaging of their drug products. Simultaneously, easy accessibility of these innovations has provided means to copy the packaging of leading pharmaceutical brands, giving rise to counterfeit/spurious products. This computer technology has made the task of copying the labels/cartons of reputed pharmaceutical companies so effortless and accurate that it is difficult to differentiate between the original and the fake.

Counterfeiters put labels of firms which may not even exist on the packaging of their drug products, so as to bypass the penal action by administrative and law enforcement agencies. Another ploy is to use the name of one drug in a class to label another drug in the same class which is cheaper—for example, ciprofloxacin tablets are labelled as levofloxacin tablets.

There may be cases where the manufacturer does not have any intention of undue monetary benefits, yet the product can be of substandard/spurious/adulterated quality. Sometimes inadvertent error in the manufacturing process leads to genesis of substandard/spurious quality products. There could be a stability problem on ageing or a formulation may be unstable at the manufacturing stage—for example, formulations containing vitamins, antibiotics, etc—where due care towards inherent stability of the API is not given before the start of process, leading to an unstable final product. Even the improper/faulty storage of such sensitive drugs in the retail/wholesale chemist shop may alter their quality to the risk of the patient. Yet in other cases there may be non-uniform mixing of the active ingredient with the excipients because of faulty mixing procedure. This problem is usually seen in cases where the quantity of active ingredient is very small compared with the total bulk in the mixer (for example, bethamethasone/dexamethasone).

CONSEQUENCES OF THE USE OF SPURIOUS AND COUNTERFEIT DRUGS
The consequences of the use of counterfeit and spurious medicines may vary from therapeutic failure to occurrence of serious adverse events and even deaths. In the case of anti-infectives, development of drug resistance is the major threat. For diseases that are treated with combination therapy—for example, falciparum malaria, tuberculosis, and HIV—poor quality drugs risk the spread of resistance. More than 30 children died in 1998 due to consumption of a cough syrup containing diethylene glycol. More than 10 patients lost their lives after receiving doses of impure glycerine at JJ Hospital Bombay in 1986. In such a scenario there is huge financial loss for the companies producing the genuine product. Contamination of, or substitution in, medicines of diethylene glycol has occurred in many countries including Argentina, Bangladesh and Nigeria, resulting in the loss of over 500 lives.

Therapeutic failure or adverse events result in loss of confidence in the health system and the systems of drug control and enforcement. The reputation of the original product is damaged and the pharmaceutical companies which invest huge resources in developing innovative products suffer financially. The state also loses revenue from the taxes and duties that would be payable on the legitimate product.

Developing countries with lax regulatory environments for drugs are also disadvantaged in their ability to attract direct foreign investment.

MANAGEMENT OF THE PROBLEM
Though Noam Chomsky, the well known American thinker, has suggested that strict drug price control along with subsidies to pharmaceutical companies will abolish the economic incentive for counterfeiting, this approach may not be a pragmatic one, especially for developing countries with limited financial resources.

The fight against counterfeit drugs requires multipronged, multisectoral, multidisciplinary transborder cooperation at the macro level and strict regulation, enforcement, awareness and vigilance at the micro level. It requires all stakeholders to contribute in order to be successful. From the perspective of developing countries, it is essential that this fight does not lead to an escalation in the prices of drugs, or the unavailability of low cost sources of bulk drugs.

Drug quality monitoring
It is the responsibility of the state, through its regulatory agencies, to ensure the availability of quality medicines to the public. A critical component in the monitoring of the drug supply by drug regulatory authorities is to maintain surveillance over the possible movement of spurious/counterfeit drugs and to investigate such cases promptly and judiciously. The quickest, cheapest and easiest way is to compare the printing, shape, embossing, taste, odour and consistency of a suspected sample with a genuine product. However, the state should ensure wide and easy availability of testing facilities to allow comprehensive and widespread surveillance and drug monitoring. In India, the Mashelkar Committee report in 2003 said that only 15 states had functioning testing laboratories and out of these only seven were well equipped; 11 states had no drug testing facilities.

Monitoring of drugs through the supply chain
Regulatory authorities and manufacturers should be able to track drugs all the way through the supply chain until they reach the customer. Italy has shown the way in this regard. Since 2001 every package carries a quality stamp which has a batch number that allows the product to be traced. The US Food and Drug Administration (FDA) has recommended that pharmaceutical companies start using “track and trace technology” and product authentication technologies to provide a
greater level of security for drug products. Radiofrequency identification (RFID) is a promising technology to meet this need. RFID technology uses a tiny radiofrequency chip containing essential data in the form of an electronic product code (EPC). Implementation of RFID will allow supply chain stakeholders to track the chain of custody of every package of medication. By assigning each discrete product unit with unique electronic serial number, every product could be traced electronically.25 The concept of “pedigree”, borrowed from the fine art trade, may be very effective in tracking drugs through the supply chain. Pedigree is defined as a statement of origin that identifies each prior sale, purchase, or trade of a drug, including the dates of the transactions and the names and addresses of all the parties involved.30 It remains to be seen how technologies such as these can be made cost effective in developing countries.

Technological innovations
In addition to track and trace technology, other authentication technologies such as barcoding, blister packing, complex holograms and logos, colour shifting ink, and taggants or chemical markers imbedded in a drug or its label are being used by manufacturers.3 32 Another technique called spatially offset spectroscopy may find a role in surveillance, as it allows verification of the chemical composition of drugs in closed blister packs and bottles using hand held devices.34 But it is necessary that manufacturers and authorities stay a step ahead by being proactive in technological innovation and adoption to prevent counterfeiting. Ghana has taken a lead in introducing a mobile based technology which brings consumers and producers in touch directly. All products are embossed with a unique code for verification of the chemical composition of drugs in closed blister packs and bottles using hand held devices.34 It is necessary that manufacturers and authorities stay a step ahead by being proactive in technological innovation and adoption to prevent counterfeiting. Ghana has taken a lead in introducing a mobile based technology which brings consumers and producers in touch directly. All products are embossed with a unique code for verification of the chemical composition of drugs in closed blister packs and bottles using hand held devices.34

Enforcement of laws and legislation
It is known that most countries have enacted sufficiently tough laws to penalise counterfeiters; lacunae lie in their implementation.6 A strong political will is a prerequisite for implementation of laws, especially in developing countries where strong judicial, administrative, managerial and policing systems are not yet in place.

Central drug regulatory authorities need to be set up in countries where they do not exist. To be effective these regulatory authorities should be equipped not only with adequate human and material infrastructure but also with legal and administrative powers against counterfeiters.

Enforcement also requires close cooperation between different branches of government including drug regulatory authorities, police, judiciary, customs and intelligence leading to effective investigation and prosecution.

In India, the government constituted an expert committee under the chairmanship of Dr RA Mashelkar to examine all aspects of regulatory infrastructure and the extent and problem of spurious/counterfeit drugs in the country.17 26 The main recommendations made by the committee were: (1) strict vigilance must be maintained, with regular surprise checks at the pharmacies; (2) provision of quality testing facilities for the drugs; (3) spurious drug offences should be made non-bailable and cognisable offences and the prosecution may be instituted by any police or CBI (Central Bureau of Investigation, India) officer not below the rank of a sub-inspector; (4) formation of a strong, well equipped and professionally managed CDSCO (Central Drugs Standards Control Organization), which could be given the status of central drug administration.

The Indian officials are taking a tough stand against counterfeit drugs. The drug controller’s office will initiate a study which will inspect around 31 000 drug samples.37

The main problem in India is that although laws exist, they are rarely implemented in letter and spirit. The penalty for counterfeit drug manufacture in India is imprisonment for not less than 3 years and a fine of 5000 rupees (US$108; €80; £75).39 This size of fine is very small compared to the profits to be made in this trade.

Awareness and vigilance
It is important to educate all the stakeholders—doctors, pharmacists, traders, marketing personnel, manufacturers as well as the public at large—about the problem of counterfeit drugs. The FDA and the National Consumers League of the USA have developed a highly informative website giving information about counterfeit drugs to the consumers. Through the Med Watch Program health professionals can report suspected counterfeit drugs to the FDA. The FDA hotline would quickly respond to reports of suspected drugs.32 Similar initiatives can be successfully replicated in developing countries including India.

In India some non-governmental organisations have developed ways to tackle the problem of counterfeit drugs. The Organization of Pharmaceutical Producers of India (OPPI) is a group of pharmaceutical manufacturers working with the International Federation of Pharmaceutical Manufacturers Association and the Pharmaceutical Security Institute (Geneva, Switzerland) to set up an intelligence network to counter the counterfeit drugs trade. Similarly, the Indian Pharmaceutical Alliance (IPA)—a group of some pharmaceutical manufacturers—have hired two top retired police officials to help deal with the problem.30

A problem area in vigilance is the reluctance on the part of pharmaceutical companies to openly communicate the data regarding the epidemiology of counterfeit drugs. Information collected by the Pharmaceutical Security Institute (Geneva, Switzerland) is not open to the public and is not even open to the participating companies.37 The ostensible reason is so as not to alarm the consumers, which might thus prevent them from taking genuine medicines. But companies do fear loss of business and reputation on reports of counterfeit drugs being made public. Even governments are often reluctant to report counterfeiting incidents. The WHO reporting system for fake drugs received only 84 complaints from 1999 to 2002 and none from 2002 to 2004 from member countries.40 41

The pharmaceutical industry should recognise that it is in the consumers’ and their own interests to share information they collect on the prevalence of fake drugs. It should be made legally binding on all parties—whether manufacturers, authorities or individuals—to report any suspicion of counterfeit drugs to the concerned authorities so that proper action can be taken. This legal obligation should be similar to the one for reporting notifiable diseases.1 Authorities should be careful in issuing alerts and educating consumers so as not to preclude genuine use.39

Patients, physicians and pharmacists need to be aware about the packaging and appearance of drugs, and any discrepancy in the size, packaging or physical characteristics of the drug
package should be reported. A cluster of treatment failures may be due to fake drugs and also needs to be reported. It is the duty of the dealers and consumers to remain within the proper supply chain and not to go astray looking for cheaper medicines. Field sales personnel of companies also need to look out for sudden fall in sales of particular products, which may be due to supply of counterfeit drugs.

Media has a role to play as a watchdog not only for counterfeiters but also for any laxness and corruption on the part of the regulatory authorities. Nigeria has used radio, TV jingles and newspaper advertisements to inform the public about counterfeit drugs as well as exhorting people to report counterfeit drugs. The media has to be a responsible player, conveying information without causing undue alarm.

Patient education is also an important aspect in controlling fake drugs. Authorities and companies need to tell patient’s the “do’s and don’ts” while taking treatment and buying drugs, so that patients remain part of the formal supply chain.

International cooperation
As the business of counterfeit drugs transcends borders, it is mandatory for all nations to come together to fight this menace. The role of organised crime and the reported use of free trade zones for the counterfeit drug trade underlies the need for international cooperation. It is mandatory that both importing and exporting countries should be able to identify the actual origin of exported medicines. It is only possible if mechanisms of transborder exchange of information and legal and administrative agreements are in place. Essential stakeholders in this framework should include Interpol, the Organization for Economic Cooperation and Development, the World Customs Organization, the World Intellectual Property Organization, the World Trade Organization, and the WHO.35

WHO has made a start by setting up IMPACT (International Medical Products Anti-Counterfeiting Task Force). Key members of this task force are the national drug regulatory authorities and law enforcement agencies. Other stakeholders include various international organisations, non-governmental organisations, pharmaceutical manufacturers, wholesalers industry associations, patients advocacy groups, and healthcare professionals. IMPACT aims to form a coordinated network across and between countries to fight this menace. IMPACT has identified five areas for action and is working upon legislative and regulatory infrastructure, regulatory implementation, enforcement, technology, and communication to achieve its goal.41

WHO also set up a rapid alert system in the Western Pacific regional office in 2005, with plans for similar efforts all over the world. Its role lies in rapid dissemination of important information to the relevant authorities for quick action.42

CONCLUSIONS
Counterfeit and spurious drugs are a big challenge to the health care system worldwide. Poverty, lack of drug regulation and legislation, and light penalties makes this a flourishing business in the developing countries. Availability and use of such drugs not only leads to therapeutic failure but also to development of drug resistance. To achieve the goal of health for all, the menace of counterfeit drugs needs to be controlled. A strong political will, an efficient regulatory environment, and enforcement of rules and laws are keys in combating this phenomenon. In a rapidly globalising world, international cooperation is necessary in order to counter this menace effectively.

The counterfeit drug industry and regulatory and enforcement conditions in India should be of concern to the world at large, as reports show India to be a major producer of counterfeit drugs in the world. It should also be of concern to the Indian pharmaceutical industry and government as it can be injurious to their reputation, and adversely affect India’s rapidly growing pharmaceutical exports.

Competing interests: None declared.

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Key messages
- Counterfeit drugs are a worldwide menace but developing countries are especially vulnerable.
- Differentiation needs to be made between counterfeit and spurious drugs.
- Developing countries including India are major producers as well as consumers of counterfeit drugs.
- High price of drugs, poverty, poor supply chain, ineffective regulations and enforcement are major factors in the spread of counterfeit drugs.
- Active pharmaceutical ingredient, inactive ingredients/ excipients and packaging are manipulated by counterfeiters.
- Major consequences of the use of counterfeit drugs are therapeutic failure, development of resistance to anti-infectives, loss of confidence in the health system, and revenue loss to nation states.
- Management of the problem requires a multipronged attack including elements of proper regulation and monitoring, legislation and strict enforcement of laws, supply chain management, technical innovations, awareness and vigilance, and international cooperation.

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