Pharmaceutical counterfeiting

Anil K. Deisingh

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Pharmaceutical counterfeiting is becoming a serious problem both in developed and developing countries. This paper considers the extent of the problem and provides several examples of drugs which have been counterfeited. Additionally, the effects of counterfeit products on consumers, health care providers, drug manufacturers and governments are discussed. Several of the currently used methods of detection are described and these include near-infrared spectroscopy, Raman spectroscopy, isotopic characterization, tensiography, chromatographic and mass spectrometric approaches. Finally, anti-counterfeiting measures such as the use of holograms, tracers and taggants and electronic tracking are summarized.

I. Introduction

The counterfeiting of pharmaceuticals has been detected since about 1990 and, recently, the problem has escalated. Many more cases are appearing, not only in the developing world but, increasingly, in developed countries. Several countries have their own definitions as to what constitutes a counterfeit drug and there is no consensus. Thus, Pakistan, Nigeria, the United States, Brazil, Portugal, Australia and Japan all have differing interpretations. This poses a problem in that what may be considered a counterfeit product in one country will not necessarily be so in another country.

The World Health Organization (WHO) has defined counterfeit drugs as those which are "deliberately mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products with counterfeit products including drugs with the correct ingredients or with the wrong ingredients; without active ingredients, with insufficient active ingredient or with fake packaging."[1] How do other countries define counterfeit medications? US law defines counterfeit drugs "as those sold under a product name without proper authorization. Counterfeiting can apply to both brand name and generic products, where the identity of the source is deliberately and fraudulently mislabelled in a way that suggests it is the authentic approved product. Counterfeit products may include products without the active ingredient, with an insufficient quantity of the active ingredient, with the wrong active ingredient, or with fake packaging."[2] Similarly, the Nigerian National Agency for Food and Drug Administration and Control (NAFDAC) has identified counterfeit drugs as those with the same quantity of active ingredient as the genuine brand ('clones'), those with insufficient or no active ingredients, expired medicines, herbal preparations that are toxic or ineffective and medicines which do not bear the name and address of the manufacturer. Clones usually hide behind fast-moving products to ensure rapid profits without the liabilities of the genuine manufacturer.[3]

The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) has estimated that 7% of all drugs sold around the world are counterfeits.[4] Furthermore, they have suggested that the value of this trade is more than USD 30 billion. In Russia, the figure has been put at 12% while in the Ukraine it may be as high as 40%.[3] The WHO has indicated that India is responsible for about 35% of the world's counterfeit medicines with the business being worth USD 200 million.[3]

The WHO has been collecting information about counterfeiting activities since 1984 and the counterfeiting of medicines was first mentioned at a WHO Conference of Experts on the Rational Use of Drugs in Nairobi, Kenya in 1985.[3] Between 1984 and 1999, there were 771 reports of counterfeit drugs with 78% of these coming from developing countries. Since that time, however, there has been a shift in the trend in that developed countries are now affected. From January 1999 to October 2000, 46 reports of counterfeit drugs were received from 20 countries; 60% from developing countries and 40% from developed nations.[3]

The number of cases of counterfeit drugs being investigated by the US Food and Drug Administration (FDA) has quadrupled from an average of five per year in the 1990's to about 20 per year in 2001 and 2002.[5] It has been reported that

Anil K. Deisingh

Anil Deisingh is a graduate of the University of the West Indies, Loughborough University, University of Massachusetts and the University of Toronto. He pursued his PhD in biosensors at Toronto under the supervision of Professor Mike Thompson. After this, he spent one year as a postdoctoral fellow at McMaster University working on the development of sol–gel enzyme assays. Currently, he is employed as an Analytical Chemist at the Caribbean Industrial Research Institute in Trinidad and Tobago. In April 2004, he was involved in organizing the first Caribbean Conference on Pharmaceutical Counterfeiting. His current research interests are in biosensors, indoor air quality and biodegradability.

prescription drug corruption is rampant among wholesalers in Florida, this being the instigator of the FDA's national counterfeit drug initiative. This allows counterfeit drugs to enter the system as they are being manufactured and distributed by large, well-organized criminal networks.[5] In the United Kingdom, the majority of counterfeit medicines are found in the illegal supply chain although counterfeit Cialis™ tablets and Reductil™ capsules were discovered in the legitimate supply chain in August and September 2004 respectively.[6] These examples represent the first cases of counterfeiting in the legal chain for over a decade.

A recent report from the International Pharmaceutical Students' Federation[7] has indicated that some drugs are more counterfeited than others. High-consumption, expensive and innovative drugs along with well-established generic drugs are most readily affected. The main categories include antibiotics, anti-protozoals, hormones and steroids, although any therapeutic class may be copied. Furthermore, it is known that almost everything connected with the drug manufacture process is being counterfeited *viz.* active ingredients, dosage forms, package inserts, packaging, manufacturers' names, batch numbers, expiry dates and documentation relating to quality control.[4]

II. Counterfeiting examples

Numerous examples of drug counterfeiting in different countries are summarized in Table 1. Even in countries where there is no widespread counterfeiting, there are examples of sub-standard products (*i.e.* those not containing the correct amounts of active ingredients or being subject to poor manufacturing practice) in the marketplace. For instance, the United Kingdom has experienced clones of Viagra™ (sildenafil citrate).[3] These include products containing caffeine and tablets resembling the branded product but, upon investigation, were found to be bulked with lactose and re-compressed to form tablets containing 30 mg sildenafil.[3]

Dr Ged Lee of the Medicines and Healthcare Products Regulatory Agency (MHRA) has identified a further problem with cloned products. Countries such as India and China do not recognize European patent laws and can legally manufacture drugs which are illegal in the UK. Thus, imitation Viagra™ products under brand names such as Penagra, Kamagra and Powergra have been seen. Each of these contained sildenafil. These products are licensed in the country of origin and can therefore be legally imported into the UK for personal use. Additionally, there has been a case where counterfeit Viagra™ was packaged in a screw-cap container, similar to the US product, except that the UK product is strip-packaged.[3]

Table 2 shows the main types of drugs which are counterfeited and is based on reports received by the WHO from January 1999 to December 2002.

III. Effects of counterfeits

The counterfeiting of pharmaceuticals has serious consequences for consumers, health care providers, drug manufacturers and governments.[10]

Consumers can be affected when there is illness or death, as has already happened on several occasions in the developing world. Additionally, due to lost revenue, exposure to huge damage claims (especially in the USA) and higher insurance rates, consumers will be subject to higher prices for drugs.[10]

Health-care providers are in a particularly difficult situation as there can be a decline in confidence in public health systems, health care professionals and in government agencies involved

Table 2 Main types of counterfeited drugs[8] (January 1999–December 2002)

Category of drugs	Percentage of total counterfeits
Antibiotics	28
Hormones and steroids	18
Anti-asthma and anti-allergy	8
Anti-malarial	7
Analgesics and anti-pyretics	6
Others (14 therapeutic classes)	33

Table 1 Examples of counterfeited drugs[4,8]

Country and year	Counterfeiting problem
Nigeria, 1990	Cough mixture was diluted with a poisonous solvent leading to the deaths of 100 children.
Mexico, 1991	Anti-burn ointment contained sawdust.
Turkey, 1993	A pharmacist is arrested after the active ingredient in 'drugs' exported to Africa was found to be baking powder.
Niger, 1995	A meningitis drug contained only water.
Haiti, 1996	59 children die after taking a counterfeit syrup for fever.
Kenya, 1998	Anti-malarial drugs were found to be ineffective.
India, 1998	Diethylene glycol poisoning killed at least 30 children.
Brazil, 1998	Ineffective contraceptive pills resulted in unwanted pregnancies.
Malawi, 1999	*Africa Health* journal reports an influx of counterfeit drugs into the country.
Italy, 2000	240 000 packs of medicines and 2 t of raw materials seized.
China 2001	The *Shenzhen Evening News* reports that more than 100 000 people died of fake drugs in 2001.
USA, 2001	Counterfeit *Serostim*, *Neupogen* and *Nutropin AQ* discovered.
India, 2001	Police found 660 kg of fake drugs, 1000 kg of raw materials and boxes bearing the logo of a reputable firm. All of these were discovered in one factory.
Nigeria, 2002	The head of the country's drug control agency reported that 60% of the drugs are counterfeit, substandard or expired.
USA, 2002	The FDA reported 3 lots of counterfeit Combivir.
China, 2002	Counterfeit drugs valued at USD 57 million were identified.
USA, 2003	Recall of 200 000 bottles of the anti-cholesterol drug, *Lipitor*[9]

in distributing drugs. In the USA and several other countries, there is greater possibility of litigation against health care professionals should consumer illness or death occur. These workers will "need to prove that they have taken every step possible to protect the integrity of the pharmaceuticals they administer."[10]

Drug manufacturers face similar issues to those described above especially with respect to liability and the potential for lawsuits. Adam Scheer of American Bank Note Holographics Inc. has described the situation as follows:[10] "Plaintiffs are holding drug manufacturers accountable, not only for the authenticity of the products they manufacture, but the safeguards they have put in place to prevent tampering in the field." In addition, drug manufacturers face damage to brand integrity as a single unsavoury incident can tarnish reputations for many years. Also, there is considerable lost revenue to the companies who have spent USD 500–800 million to develop a single drug.

Governments also face the critical issues of public health confidence and widespread illnesses which could strain health care systems, lost tax revenues since counterfeit drugs bypass traditional sales avenues, and increased costs of monitoring the efficacy and safety of pharmaceuticals.[10]

IV. Methods of detection

Several methods are employed to detect drugs which may be suspect while researchers are working assiduously to develop other rapid detection schemes. They range from simple thin-layer chromatography (TLC) to more sophisticated techniques such as near-infrared spectroscopy (NIR) and liquid chromatography-mass spectrometric (LC-MS) approaches.

4.1 Simple chemical approaches

Michael Green and colleagues at the Centers for Disease Control and Prevention (Atlanta, GA) and the University of Oxford have been involved in developing simple and low-cost approaches to rapidly identify counterfeit drugs in developing countries. In addition, one of their primary goals is to adapt these techniques to field testing.[11]

TLC and colorimetry are two of the most common techniques for evaluating drug quality. The former allows the active ingredient to be recognized by comparison with a known drug standard. This approach is cheap, specific and sensitive. Similarly, colorimetry is rapid and highly specific.[12] The intensity of a positive colour reaction is usually proportional to drug concentration with visual assessment allowing for semi-quantitation.[11] Usually, colour intensity can be measured by using a portable filter photometer.

Green and co-workers have developed a colorimetric test to determine the quality of the anti-malarial drug artesunate in South-East Asia.[13] A small portion of a tablet is scraped into a tube containing a base, a buffer is added followed by the reagent. A yellow colour is produced if artesunate is present.[14] A similar test has been developed for another anti-malarial drug, artemether. This group is also working on a test for mefloquine using tablet disintegration characteristics with content analysis. Counterfeit and sub-standard drugs may contain the required amount of active ingredients but will fail the disintegration test.[11]

4.1.1 Bulk property testing. Bulk properties of matter include weight, density, solubility, viscosity, refractive index and optical rotation, as well as physical description of the tablets. These can be easily measured by low cost, rugged equipment and can provide simple tests for detecting counterfeit drugs.[11]

Green's group have used refractive index (RI), solubility, pH and crystal morphology to differentiate counterfeit from genuine artesunate tablets. Briefly, the method involved weighing and pulverizing the tablet before suspending it in alcohol. The filtered tablet extract is used to perform the various analyses. Comparisons were made with chloroquine, aspirin and acetaminophen tablets, all of which are of similar size, weight and shape to artesunate tablets. Genuine tablets had a pH of about 3.5 while counterfeit artesunate, chlroquine and acetaminophen were 6.5 with aspirin having a pH of 2.0.[11] Solubility was determined by adding the alcoholic extract to water and a light meter was used to measure precipitation as a function of attenuated light transmission through the sample. By plotting the number of sample drops *versus* signal (light transmission), it was possible to distinguish the genuine product from counterfeits. The former gave a milky product while the counterfeit samples gave either hazy solutions or very dense precipitates.[11] Crystal morphological studies were carried out by allowing crystals to settle out after standing for a few hours at room temperature. Genuine samples showed rod-shaped crystals while the other samples did not crystallize.

Refractive index measurements can allow quantitative results to be obtained. The refractometer is a simple, portable instrument which utilizes the principle of refraction. Differences in RI values, after correction for a blank, were multiplied by two conversion factors: artesunate specific conversion and excipient compensation factor. The results of the evaluation of 33 tablets showed sensitivity and specificity were 83% and 90% respectively.

4.2 The GPHF mini-lab

The German Pharma Health Fund (GPHF), an initiative of the research-based pharmaceutical companies in Germany, has developed some simple test methods to detect counterfeited and/or substandard products. The methods were developed in co-operation with the School of Pharmacy and the University of Bonn and the Department of Tropical Medicine at the Mission Institute in Wuerzburg in Germany.[15] The Minilab was subject to testing in the Phillipines, Kenya, Ghana and Tanzania in 1997 and 1998 which confirmed its effectiveness for identification of pharmaceutical products.

A four-stage process is used to test for the quality of drugs:[15]

(a) visual inspection of solid dosage forms and packaging material;

(b) tablet and capsule-disintegration test for a preliminary assessment of any deficiencies related to drug solubility;

(c) simple colour reactions to identify drugs;

(d) semi-quantitative TLC to check for quantities of drug present.

The GPHF Minilab has all the apparatus required for testing fit into two standard suitcases with a total weight of 40 kg. This allows it to be used in the field with other advantages being low cost (USD 4000), reliability and versatility. Each Minilab has enough reagents to perform 3000 colour-reaction identity tests and 1000 TLC experiments.[15] Some of the drugs which can be identified include acetylsalicylic acid, amoxicillin, artesunate, chloramphenicol, furosemide, isoniazid, metronidazole, quinine and tetracycline.[16] Up to late 2003, there were 127 Minilabs in operation around the world, with the majority being in Africa and Asia.

4.3 Chromatography and mass spectrometry

These two areas have been widely used for more than thirty years for the detection of counterfeit pharmaceutical products. Drug profiling is necessary to determine the impurities which may be present in the active ingredients. This is used to determine the source of raw materials used as well as the synthetic route employed.

4.3.1 Chromatography. Gas chromatography (GC) has been utilized for confirming essential oils, residual solvents (head space analysis), volatile constituents (especially from herbal medicines) and undeclared ingredients. High-performance liquid chromatography (HPLC) has been useful for profiling of herbal substances, detecting adulterants and for determining the presence of organic residues.[17] Official laboratories around the world use these methodologies to detect counterfeit medicines. Thin layer chromatography (TLC) has also been used for the identity testing of a second series of drugs from the Essential Drug List (acetylsalicylic acid, paracetamol, ibuprofen, dexamethasone, prednisolone, hydrocortisone) and for betamethasone, metamizol and hydrocortisone acetate.[18] Additionally, TLC in tandem with UV spectrometry and microcrystal tests with saturated aqueous picrolonic acid and 5% aqueous mercury(II) chloride was used to detect and identify phentermine (Ionamin®) adulteration. The counterfeit capsules contained only caffeine and phenylpropanolamine.[19]

Apart from GC and HPLC approaches, capillary electrophoresis (CE) has been utilized to detect trace components in bulk pharmaceutical products.[20] The emphasis was on the identification of differences among various manufacturers which could be used for source verification in suspect and/or counterfeit cases. Micellar electrokinetic capillary chromatography (MECC) with sodium dodecyl sulfate (SDS) was employed to analyse β-lactam antibiotics. The aminoglycoside clindamycin phosphate and the macrolide erythromycin stearate were analysed using borate buffers with direct UV detection. The determination of product potency using peak area ratios was demonstrated for ampicillin and clindamycin phosphate.[20]

Recently, HPLC along with GC-MS was used to detect a Viagra™ mimic tablet containing amphetamine in Hungary.[21] Except for the pink colour, the tablet appeared to be genuine (which is blue). Analyses by GC-MS and HPLC showed that sildenafil citrate, the active ingredient in Viagra™, was not present. Instead, 15 mg of amphetamine was detected.

Counterfeit metylphenidate (Ritalin™) tablets were detected by GC-FID (flame ionization detection) and GC-MS at the California Bureau of Forensic Services Laboratory. These two methods showed the presence of oxycodone with a trace of dihydrocodeinone rather than methylphenidate in the tablets.[22]

The analysis of organic volatile impurities is a useful tool for the examination of bulk pharmaceuticals. This allows the detection of counterfeit drugs as well as tracing their source.[23] The determination of residual solvents and other organic volatile impurities (OVI's) can assist this process. Static headspace analysis combined with GC-MS can be used to detect and determine volatile impurities. This approach was successfully employed to detect sulfamethazine, ranitidine hydrochloride and doxycycline hyclate.[23] In each case, it was possible to distinguish one source of the product from another by differences in the organic volatile impurities present.

4.3.2 Mass spectrometry. Mass spectrometric (MS) techniques have also been widely used to characterize pharmaceutical products. Emphasis has been on time-of-flight (TOF) approaches with electrospray ionization (ESI) detection being commonly employed in drug profiling.

TOF-secondary ion mass spectrometry (TOF-SIMS) has been used for the analysis of bulk polymeric films which are utilized as either biomaterial coatings or as drug delivery vehicles. However, the method can also be employed to characterize pharmaceuticals by analyzing the entire drug dosage form.[24] This information allows for the development of drug delivery systems and also allows the patent holder to defend itself against counterfeiting. TOF-SIMS in co-operation with imaging techniques was used to investigate the distribution of excipient, drug and polymer layers within multiplayer controlled-release pellets.[24]

Recently, Belgian researchers evaluated a TOF mass spectrometric detector, equipped with an electrospray LC-MS interface for a comprehensive drug profiling analysis. An automatic MS to MS/MS switching function was incorporated and it was reported that the method possesses potential for profiling especially as up to eight different ions can be simultaneously selected for MS/MS if they reach preset criteria.[25]

4.3.3 Hyphenated techniques. Hyphenated techniques such as gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) and variants of these have been used to assess the quality of drugs.

Pyrolysis-gas chromatography-mass spectrometry, along with pattern recognition techniques, was used to discriminate between tablet production methods.[26] The two methods of wet granulation and direct compression can be differentiated by deconvoluting the py-GC-MS data of each sample into concentration profiles and spectra, followed by construction of a matrix with each compound corresponding to one column. The principal components are kept after excluding variables and processed by Fisher discriminant analysis. Finally, the data are assigned to classes by the use of unsupervised and supervised classification methods. This approach had a correct classification rate of 85%, which may

make it useful in determining the source from which a tablet is derived.

A recent paper by Glaxo SmithKline researchers described the analysis of betamethasone, dexamethasone and similar compounds by LC-electrospray MS (HPLC/ESI-MS). The method differentiated the epimers and various esterification products in counterfeit drugs. Good separation with baseline resolution of all epimers/isomers was obtained on the column using a step gradient with mobile phases of ammonium acetate and acetonitrile. Betamethasones can also be distinguished by the relative abundance of the *m*/*z* 279 ion in the spectra.[27]

Similarly, various MS techniques were applied towards the identification of active ingredients in a counterfeit Halfan™ drug product.[28] This anti-malarial drug was analysed by accurate mass electrospray ionization mass spectrometry, accurate mass tandem mass spectrometry (MS/MS) and LC-MS. Tandem mass spectrometry allowed identification of parts of the molecule from fragments which limited the number of possible elemental compositions for the active ingredient in the counterfeit product. LC-MS separation and reference MS/MS allowed further identification of the active ingredient in the counterfeit product. The active ingredient turned out to be sulfamethazine, an antibacterial compound.

ICP-MS (inductively-coupled plasma-mass spectrometry) for elemental profiles and ion chromatography for anion/cation profiles can also prove useful in the detection of counterfeit pharmaceuticals. Recently, Waddell and co-workers[29] reported on the use of ICP-MS to analyse ecstasy tablets to provide linkage data from seizure to seizure. In this case, the data was analysed by statistical methods such as principal component analysis and artificial neural networks.

4.4 Near-infrared spectroscopy

The infrared spectrum is divided into three regions: near-, mid- and far-infrared radiation.[30] Although the majority of analytical applications have been in the mid-infrared region, an increasing number of applications in the near infrared region are being reported.

NIR spectroscopy has been used for various applications in the pharmaceutical industry. These include the identification of pharmaceutical raw materials and final products[31] and determination of the content of the active ingredients in drugs.[32] One of the first papers to report on the use of NIR spectroscopy for the identification of counterfeit drugs was that of Scafi and Pasquini in 2001.[33] The identification was based on the comparison of the NIR spectrum of a sample with typical spectra of the authentic drug using multivariate modelling and classification algorithms, such as principal component analysis (PCA). NIR spectroscopy was evaluated for spectrum acquisition of various drugs which were selected in order to observe the many physico–chemical characteristics found among commercial products.[33] Fig. 1 shows the reflectance spectra of the drug "Femme" and the differences between the real and counterfeit samples. Additionally, the parameters which could affect the spectra of a drug were investigated with the results demonstrating that the first derivative can minimize spectral changes associated with tablet geometry, physical differences in their faces and position relative to the probe beam.[33] It was found that NIR spectroscopy was able to rapidly and non-destructively identify counterfeit pharmaceuticals such as Combiron® (ferrous sulfate), Aldomet® (methyldopa), Floxacin® (norfloxacin) and Tylenol® (acetaminophen) amongst others.

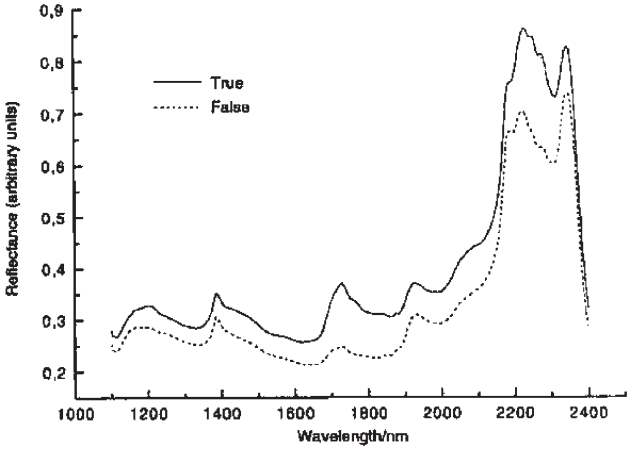

Fig. 1 Reflectance spectra of the drug Femme™ and the differences between the real and counterfeit samples. (Reprinted from ref. 33 by permission of The Royal Society of Chemistry.)

The main advantages of NIR spectroscopy are:[32] (a) it is a non-destructive method, (b) it is both qualitative and quantitative and (c) it provides fingerprints of the whole matrix. The main drawbacks with this method for drug identification are humidity changes, sample position and, for tablets, sample face.[34] These parameters need to be controlled for the results to be acceptable.

Anthony Moffat's group at the University of London School of Pharmacy has been using NIR spectroscopy to detect counterfeit medicines.[17] They have found the method is ideal for analyzing excipients (*i.e.* non-active ingredients), which, in most cases, make up the bulk of a tablet with a notable exception being paracetamol. Although counterfeit drugs may contain active ingredients in the correct proportion, the excipients may not always be at the same concentration as that used by the trademark owner. Moffat has indicated that a careful examination of the excipients will indicate if the drug was genuine.[17] However, physical differences between tablets from different manufacturers will need to be removed by mathematical pre-processing techniques such as standard normal variate (SNV) or PCA methods. The former can distinguish differences in moisture content while the latter can be used to differentiate tablets from different sites.

The combination of NIR with microscopy may provide further information about the composition of a tablet. New NIR-imaging techniques can scan the surface of a tablet in just 20 min.[17] Additionally, the combination of NIR-microscopy with Raman-microscopy can provide complementary information about excipients.[17] These hybrid imaging techniques can identify and quantify excipients, assess the particle sizes and measure the homogeneity of the mix. Further information on hardness, compression, dissolution and moisture can also be obtained.[17] This approach has been successfully used by Moffat to identify counterfeit Viagra™ tablets.[35] However,

there are still problems of uniformity of results and the need for authentic specimens for comparison.

In a related development, scientists at Perkin-Elmer (Shelton, CT) have developed a Fourier transform-NIR (FT-NIR) imaging system which can identify counterfeit drugs based on differences in the distribution of ingredients within the product.[36] This may be caused by different blending processes or differences in the ingredients which could be in fine powder, fine crystalline or coarse crystalline form. Spectra were collected between 7800 and 4000 cm^{-1}, using 16 cm^{-1} spectral resolution. The distribution of caffeine is homogeneous in the authentic product but localized in the counterfeit product, reflecting different manufacturing processes.[36] However, the method has yet to undergo the type of testing that NIR spectroscopy has already proven itself capable of doing successfully.

4.5 Raman spectroscopy

Raman spectra are obtained by irradiating a sample with a powerful laser source of visible or infrared monochromatic radiation. During the irradiation process, the spectrum of the scattered radiation is measured at an angle, usually 90°, with a spectrometer.[37] Over the last decade, it has been suggested that Raman spectroscopy is a useful method for the screening of seized tablets and powders for illicit substances.[38,39] The two major reasons put forward are: (a) the ability to record spectra without sample preparation and (b) the short (less than a minute) collection times required.[40]

Researchers at Queen's University (Belfast, UK) and the Forensic Science Agency of Northern Ireland have shown that Raman spectroscopic methods can be used to distinguish between ecstasy (MDMA, 3,4-methylenedioxymethylamphetamine) and various other phenethylamine ecstasy analogues.[41] Even when mixed with excipients, it is possible to identify the compounds (Fig. 2). This rapid identification of the active drug is useful but it is possible to obtain even more information from the Raman spectrum. This includes such features as identification of excipients, the relative concentration of drug to excipient and the degree of hydration of the active compounds.[40] This detailed information is referred to as 'composition profiling'. The spectra obtained in such cases are rich in vibrational bands and allow the active drug and excipient to be identified. Relative band heights can be used to determine drug : excipient ratios and the degree of hydration. In this study, 400 tablets from a seizure of more than 50 000 tablets were examined. Despite some tablet-to-tablet variation, the contents could be classified on the basis of the excipients used *e.g.* sorbitol, glucose or cellulose. This study showed that simple physical description coupled with active drug content do not fully characterize the nature of the seized tablets mainly because of a single seizure of physically similar tablets was studied.[40]

A further study on a larger scale (1500 tablets) has been conducted and, as before, significant differences in the Raman spectra, due to variation in both the nature and concentration of the excipients used, were observed.[42] The ratios of the peak heights of the prominent drug bands and the drug band against the largest excipient band in the spectrum were measured for all the samples. Matches between batches of tablets from different seizures were significant.

These studies show that Raman spectroscopy is a rapid and non-destructive method for tablet analysis. There is little difficulty in obtaining good quality data with a simple dispersive instrument using red (810 nm) excitation and accumulation times of 40 s.[40] Furthermore, sample preparation is not onerous and it is possible to analyse up to 50 tablets in 1 h. However, there is the problem that homogeneity is not guaranteed. This inhomogeneity can cause problems if microscopic illumination and/or collection is used because, for every tablet, a series of spectra will need to be taken at

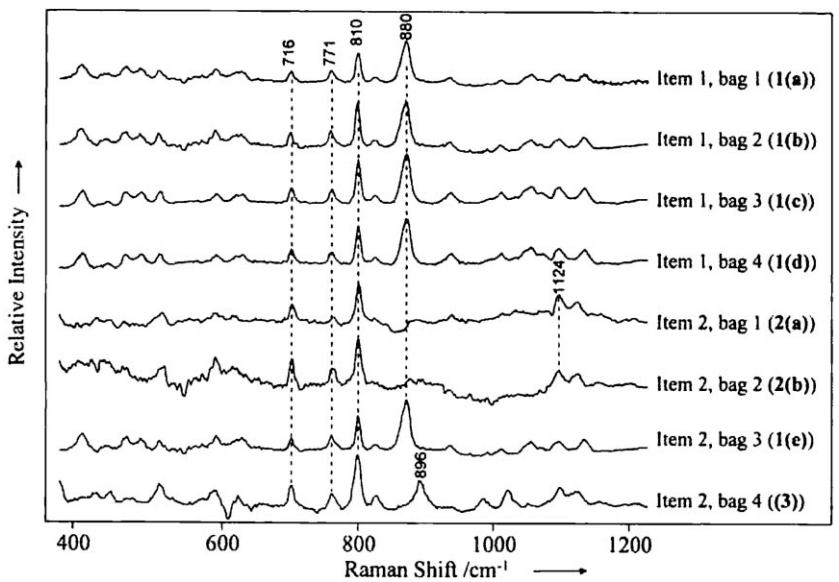

Fig. 2 The averaged Raman spectra of 6 tablets randomly selected from each of 8 large bags of tablets in a seizure. The strongest MDMA bands are at 716, 771 and 810 cm^{-1}, the strongest excipient band in each of the spectra is also labelled. The excipients are: Samples 1 (a)–(e) sorbitol; 2(a) and (b) cellulose; and sample 3 glucose. (Reprinted from ref. 40 by permission of The Royal Society of Chemistry.)

different points on the surface to ensure the data are representative of the composition of the sample.[41] Although controlled substances are considered here rather than pharmaceuticals, it is proposed that Raman spectroscopy will become more widely used in the pharmaceutical industry as the number of counterfeiting incidents increases.

4.6 Tensiography

Tensiography is a recently developed technique in which a forming pendant drop is illuminated from within by an optic fibre generator and receiver. The technique provides fingerprint traces whose profiles depend on surface tension, refractive index and colour amongst other parameters.[43] Tensiography allows a solution of the active molecule to be continuously sampled thus providing a continuous flow of information as the molecule passes into solution. By fingerprinting each product, the technique is capable of differentiating one supplier of drugs from another and, also, one batch from another.[43] Brian O'Rourke at the Institute of Technology Carlow (Republic of Ireland) is currently focusing on the detection of counterfeit penicillins by tensiography.

4.7 Isotopic characterisation

It has been suggested that natural stable isotopic 'fingerprints' of pharmaceuticals can be used as a specific method for detecting counterfeits.[44] Since stable isotopes are non-radioactive and exist naturally in drugs and other materials, no external reagents are required. This makes the procedure simple and attractive to the end-user. A study of four analgesic compounds indicated that individual batches of each drug could be identified on the basis of their bulk isotopic fingerprints. The samples were powdered and their $^{18}O/^{16}O$, D/H and ^{13}C ratios were measured by continuous flow conbustion/pyrolysis isotope ratio mass spectrometry.[44] Jasper has reported that the specificity of the technique is similar to that of DNA identification.[45] It has been claimed that isotopic product authenticity is currently accepted by researchers and that it is slowly gaining acceptance by quality assurance officials and pharmaceutical companies.[44] This type of identification allows manufacturers to minimize counterfeiting, counter-trading and theft because it is very expensive to counterfeit the specific isotopic composition of specific drugs.[46]

V. Anti-counterfeiting measures

Most of the anti-counterfeiting measures employed by the pharmaceutical manufacturers are concerned with maintaining authenticity of their products. Authentication can be divided into three categories:[47] (i) *overt* security features which are apparent and visible and do not require instruments to detect them, (ii) *covert* features which are hidden, not immediately apparent and which require a simple instrument (*e.g.* UV lamp, magnifier) to identify them and (iii) *forensic* level features which are very secret and are present on a 'need to know' basis only. These may include the addition of a taggant material or changes to a substrate or print which requires specialized instrumentation to detect them.

Table 3 gives examples of each type of authentication category. Several of these approaches will be described to give an overview of the methods which are currently employed.

5.1 Holograms

The use of holograms and security print features as a means of confirming genuine products has grown rapidly over the last decade.[48] Holograms are generated from the interference patterns obtained through the interaction of laser beams. The complexity of origination varies from the traditional 3D image to computer generated 2D-diffraction patterns.[48] Currently available security holograms produce 2D–3D designs, where different planes of 2D artwork will be visible at different angles.

Holograms are now widely available in a variety of formats such as:[49] (i) holographic shrink sleeves to protect branded bottled products against counterfeiting and refilling, (ii) blister packaging aluminium foil, (iii) pharmaceutical PVC, where the hologram is applied as a thin stripe to PVC sheets used to make blister packs, (iv) holographic induction cap seals, (v) polyester-based tamper evident labels used to seal packages and (vi) holographic hot stamping foil where the hologram is fused to the host surface by heat and pressure.

Advantages to the use of security holograms include the following:[10] (i) they are difficult to counterfeit, (ii) they are recognizable to the consumer, (iii) they can feature covert tools such as nanoimagery, micro-imagery, digital watermarks and hidden images, (iv) they are relatively cheap and (v) they allow the tracing/tracking of products through the distribution chain.

5.2 Tracers, taggants and inks

Additions of chemical and biological tracers to the packaging and/or product has been relatively commonplace as an anti-counterfeiting measure. According to Prebble,[48] "verification ranges from simple to complex, with certain paper systems authenticated using specially developed colour change pens." With respect to inks, many types are available and these

Table 3 Examples of authentication features[47]

Overt	Covert	Forensic
Optically variable coatings which change colour when viewing angle is changed	Microscopic particles of specific colours	Addition of low concentrations (ppm) of a taggant
Holographic foils	Labels printed with colour combinations	Identifying the isotopic composition of naturally occurring materials
Thermochromic inks and coatings	Holograms containing microtext	IR analysis
Watermarks	Inclusions with characteristic spectroscopic properties	Additions of DNA fragments to products and packaging

include UV fluorescent, phosphorescent, thermochromic and those at specific light frequencies.

To assist in the identification of counterfeits, the inks may contain security taggants of which there are four major types:[47]

(a) spectroscopic taggants which comprise inks that may be UV absorbers and may be incorporated into particles, fibres or security threads embedded into paper or packaging;

(b) biological taggants which may include strands of specific DNA. This DNA-embedded ink technology is cost-effective, the ink is difficult to replicate[50] and allows for real-time product authentication;[51]

(c) chemical taggants which include pH-sensitive and other materials which can only be detected by IR spectroscopy or X-ray fluorescence and;

(d) physical taggants such as the use of microscopic plastic particles which are only visible with the use of microscopy. Upon magnification, coloured layers or sections are detected which allows rapid authentication.

In a related approach, digital watermarking is also becoming an important authentication method. This is a technology associated with print design and it allows a characteristic to be embedded into the design without affecting the printed image.[47] However, it can be detected by a simple digital scanner. Although some watermarks can be counterfeited, generally they are impossible to remove, are machine-readable and provide good covert security features.[51]

5.3 Electronic tracking

Electronic tracking systems, such as radio frequency chips which make use of tagging of products by manufacturers, are being developed to track products through the distribution chain. Such methods are able to transmit a large volume of specific information about the product and will allow distributors and retailers to track their product when necessary.[52]

Electronic tagging using radiofrequency identification (RFID) varies in cost from a few pence to several pounds depending on data capacity, range and read/write capability of the taggant.[51] Data is stored and processed electronically to allow easy product identification. The main advantages of RFID are speed and ease of use but these are offset by the high cost of equipment.

In a recent development, it has been reported that RFID, coupled with the electronic product code (EPC, which is similar to the barcodes on supermarket products) and electronic pedigrees (secure records documenting the drug was manufactured and distributed under safe and secure conditions) are essential elements in a multi-layered approach to combating counterfeit drugs.[53] The FDA Counterfeit Drug Force, in its 2004 report, *Combating Counterfeit Drugs*,[54] has indicated that the ''use of mass serialization to uniquely identify all drug products is the single most powerful tool available to secure the drug supply. Mass serialization involves assigning a unique EPC to each pallet, case and package of drugs and then using that number to record information about all transactions involving the product, thus providing an electronic pedigree from the manufacturer to the point of dispensing.'' The EPC allows the drug purchaser to immediately determine the authenticity of the product.

VI. Concluding remarks

Many aspects of pharmaceutical counterfeiting *viz.* examples, the effects, methods of detection and anti-counterfeiting measures have been discussed in this review. However, none of these would be useful without initiatives to combat the rise in the number of cases of fake and/or substandard products on the market.

On both sides of the Atlantic, major schemes are underway to help alleviate the problem. The FDA has launched an initiative to protect American consumers from counterfeit drugs. This is designed to:[54]

(a) Better identify the risks and threats from counterfeit drugs.

(b) Establish a public and private coalition to fight drug counterfeiting and distribution.

(c) Develop new tools to aid in identifying, deterring and combating counterfeiting.

The specific approach to protect consumers from counterfeit drugs includes the following elements:[54]

(a) The implementation of new technologies to protect the drug supply of which RFID has been recommended for general use by 2007. Authentication technologies such as holograms and taggants are also recommended.

(b) Adoption of electronic track and trace technology to accomplish and surpass the goals of the Prescription Drug Marketing Act.

(c) Adoption and enforcement of strong, proven anti-counterfeiting laws and regulations.

(d) Increased criminal penalties to deter counterfeiting and more adequately punish offenders.

(e) Adoption of secure business practices by all participants in the drug supply chain.

(f) Development of a system to ensure effective reporting of counterfeit drugs.

(g) Education of consumers and health professionals about the risks of counterfeit drugs.

(h) Collaboration with foreign stakeholders to develop strategies to detect counterfeited drugs globally.

In Europe and Asia, the International Chamber of Commerce's Commercial Crime Services Unit has also developed initiatives to combat the rise in counterfeit drug cases. The Counterfeit Pharmaceuticals Initiative (CPI) was launched by the ICC at the beginning of 2003 and its remit is to collect and disseminate information both confidentially and publicly. The objectives of the CPI are:[55]

(i) The creation of a counterfeit pharmaceuticals database with online search facility.

(ii) Construction of a dedicated CPI website.

(iii) Compilation of a list of international contact points in governments, law enforcement and customs.

(iv) Liaising with regulators.

(v) Providing assistance to members by lobbying and investigation.

(vi) Special projects and surveys *e.g.* internet pharmacies.

(vii) Implementation of anti-counterfeiting technologies.

The battle against counterfeit drugs has only just begun and it will be a long road ahead for those involved in getting rid of this illegal trade. The counterfeiters are becoming more technologically savvy with the consequence that it is very difficult to detect sub-standard products. However, developing technologies such as near-infrared spectroscopy, Raman spectroscopy and isotopic characterization can prove useful in providing rapid detection methods. Furthermore, by making use of sophisticated anti-counterfeiting measures such as holograms, taggants and electronic tracking, manufacturers can trace their products from production to distribution.

Peter Lowe of the ICC's Counterfeiting Intelligence Bureau has concluded that: ''Despite existing regulatory and legal efforts, the counterfeiting of pharmaceuticals remains a very serious public health concern.''[9] This will need widespread international collaboration over the next several years to make inroads into the counterfeiter's strongholds.

Anil K. Deisingh
Caribbean Industrial Research Institute, University of the West Indies, St. Augustine, Trinidad and Tobago. E-mail: anildeisingh@aol.com

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