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A Review on Packaging Materials with Anti-Counterfeit, Tamper-Evident Features For Pharmaceuticals

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Abstract: Problems related to safety, efficacy & quality of medicines exists in many places around the world today, not just developing countries but in developed countries as well. Counterfeiting can apply to both branded and generic products and counterfeit products include products with correct ingredients or with fake packaging. Counterfeit drugs may lead to death in severe cases such as heart attack, epilepsy, angina pectoris, in such condition anti-counterfeit drugs acts as weapon to avoid tragedy. It is very difficult to identify counterfeits from genuine products. Hence anti-counterfeit packaging techniques such as 2-D barcodes, holograms & Radio frequency identification overt, or visible features, covert, or hidden markers, forensic techniques, and serialisation/track and trace can be used to protect patient from counterfeit medicines.

Keywords: counterfeit, tamper-evident, barcodes, holograms.

INTRODUCTION:

COUNTERFEIT:

According to WHO definition [1] "A counterfeit pharmaceuticals product are that is deliberately and fraudulently mislabelled with respect to identity or source. Counterfeit products may include products with correct ingredients, wrong ingredients, without active Ingredients, with the incorrect quantity of active ingredient or with fake packaging" [2].

TAMPER-EVIDENT:

A package or container that is tamper-evident is made so that you can see if someone has opened it before it is sold in the shop. Tampering involves the deliberate altering or adulteration of information, a product, a package, or system. Solutions may involve all phases of product production, distribution, logistics, sale, and use. Tamper-evident designs have been a feature of letters since ancient times, often using wax seals to signify that the letter had not been opened since it was written. Roman signet rings for example, were unique to the person who owned them, and the ring was pressed into the hot wax seal forming a signature which could not be easily duplicated by somebody attempting to re-seal the letter.

DISCUSSION:

Types of Counterfeit mechanism:

There are five different types of counterfeit mechanisms in which drugs are manufactured or

distributed without proper regulatory approval and do not meet the determined standards of safety, quality, and efficacy:

1. No active ingredient (43 %)
2. Poor quality drugs (24 %)
3. Low levels of active ingredient (21 %)
4. Wrong ingredients (2 %)
5. Wrong packaging or source (7 %) [3]

COUNTERFEITING OF DRUGS IN INDIA:

According to a report by the Organization for Economic Co-operation and Development, 75% of fake drugs supplied world over have origins in India, followed by 7% from Egypt and 6% from China[4] [Figure 1].

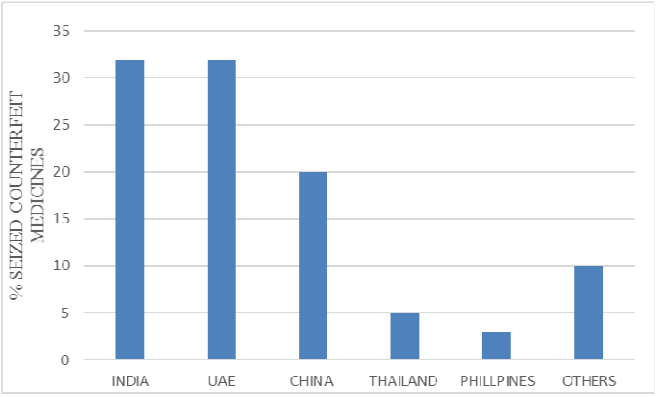

Figure 1: *Percentage of seized counterfeit medicines in different countries*

Methodology:

Anti-counterfeit packaging includes following techniques [5]

1. Serialisation/track and trace technologies
   - 1.1. Barcodes
   - 1.2 Radio frequency identification (RFID)
2. Overt Technologies
   - 2.1 Holography
   - 2.2 Colour shifting security inks and films
   - 2.3 Security graphics
   - 2.4 Sequential product numbering
   - 2.5 On-product numbering
3. Covert Technologies
   - 3.1 Invisible printing
   - 3.2 Embedded images
   - 3.3 Digital watermarks
   - 3.4 Anti-copy or anti scan design
   - 3.5 Laser codes

1. Serialisation/track and TRACK AND Trace technologies

A number of track and trace applications are under development for the pharmaceutical sector, although the principles have been established for many years in other contexts. These involve assigning a unique identity to each stock unit during manufacture.

1.1 BARCODES:

Barcodes are used in the pharmaceutical industry to identify product throughout the supply chain. Different levels of information can be carried in a barcode, including such items as National Drug Code (NDC), Lot Number, and Expiration Date [5].

2-D Barcodes are present in following formats [Figure 2].

A. Linear format

B. Scripted format

C. 2-D data matrix format

Figure 2: Linear format

Script format

Data matrix format

1.2 RADIOFREQUENCY IDENTIFICATION (RFID):

RFID is a wireless data collection technology that uses radio signals for identifying objects. The basic premise behind RFID systems is that you mark items with tags. These tags contain transponders that emit messages readable by specialized RFID readers. Most RFID tags store some sort of identification number; for example a customer number or product SKU (stock keeping unit) code. A reader retrieves information about the ID number from a database, and acts upon it accordingly and list of companies using this technology is as shown in [6] [Table1].

Table 1: List of pharmaceutical companies using RFID technology

Name of company	Product using RFID technology
Pfizer	Viagra
Purdue pharma	Oxycontin
GSK	Trizivir

Medicines have been the centre of attraction for the counterfeiters to the number of reasons listed in [Table2] and the factors responsible for the counterfeiting are shown in [Figure 3]. Maximum counterfeit reports are related to antibiotics, antiprotozoal, hormones and steroids.

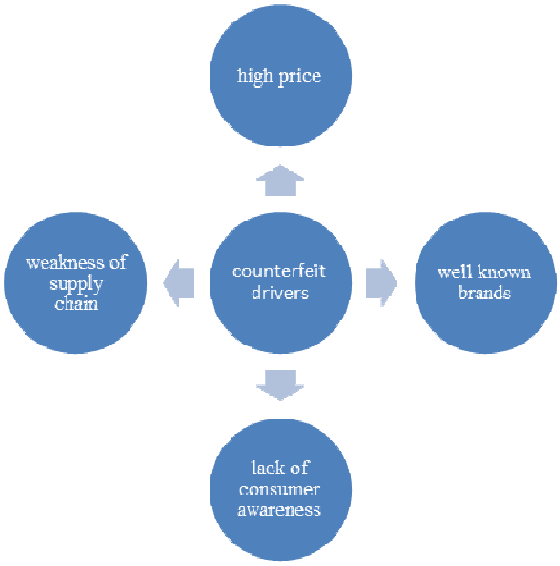

Figure 3: factors responsible for counterfeit

Table 2: COUNTERFEIT MEDICINES ACROSS GLOBALLY

COUNTERFEIT MEDICINES GLOBALLY		
Year	Country	Out come
1990	Nigeria	A cough mixture diluted with a poisonous solvent. Over 100 children died
1998	India	Di-ethylene glycol poisoning killed 30 children
2003	USA	Recall of 200,000 bottles of the anti-cholesterol drug, Lipitor.
2005	UK	A counterfeit Viagra factory was discovered in north London.
2009	Europe	More than 2 million counterfeit insulin needles were found in established European distribution channels.
2009	Kenya	Counterfeit antihypertensive and anti-diabetic drugs were seized by Kenya officials
2010	Bangladesh	Testing of 500 samples revealed that 300 were either counterfeit or of substandard quality
2010	China	A hospital has paid compensation to patients who suffered adverse effects after being treated with a counterfeit drug of Roche.

2. Overt Technologies:

Overt features enable instant authentication of packaging through visual inspection by the user without requiring expert knowledge. Optically variable features such as holographic devices within the design and colour shift inks are the most common and effective overt security features, enabling packaging to be validated both quickly and easily.

2.1. Holography

Easily identifiable holograms, showing the pharmaceutical manufacturer's logo for example, are primarily used as first level identification devices and are designed to enable successful authentication at point of inspection. Additional features, such as Nano text and hidden images, can be used as second and third level techniques for trained and equipped specialists.

High security holograms cannot be reproduced by using conventional printing methods available on the market. In addition, tiny holographic markers can be printed in a predetermined

position on the packaging. These markers are clearly visible when viewed with a magnifier, but invisible to the naked eye.

Whilst holograms offer a high level of overt security on their own, they can also be used in combination with other security devices to provide another hurdle for would-be counterfeiters to overcome, including colour shift inks [7, 8].

2.2. Colour shifting security inks

Colour shift inks appear as two or more distinct colours when viewed from differing viewing angles. Such features are easily verified by tilting the item carrying the colour-shift in order that the different colours can be seen. Different colour combinations are available and both strong opaque and subtle transparent effects can be created to complement the existing design of the packaging.

Currently, only a limited number of security suppliers produce colour-shift inks since the process to create the colour-shift pigment is highly specialized requiring particular technical knowledge and bespoke equipment. Supply of colour-shift inks is tightly controlled to ensure that the products are used only in genuine circumstances and under strict codes of conduct including end use agreements [9].

2.3. Security graphics

Fine line colour printing, similar to banknote printing, incorporating a range of overt and covert design elements such as guilloches, line modulation and line emboss. They may be used as background in a discrete zone such as an overt print area, or as complete pack graphics, and can be printed by normal offset lithography, or for increased security by intaglio printing. Subtle use of pastel "spot" colours makes the design more difficult to scan and reproduce, and security id further enhanced by the incorporation of a range of covert design elements, such as micro text and latent images [10].

2.4. Sequential product numbering

Unique sequential numbering of each pack or label in a batch can make counterfeits easier to detect in the supply chain. If printed visibly, it provides a semi-overt means of authentication by reference to a secure database, because duplicates or invalid numbers will be rejected. The main disadvantages of sequential numbering are that the sequence is predictable and easily replicated, and end users require some means of access to the database. The more secure option is serialisation by means of a pseudo-random non-repeating sequence, and this is discussed in the track and trace section [11].

2.5. On-product Marking

On-product marking technologies allow for special images or codes to be placed on conventional oral dosage forms. These overt technologies can be difficult to replicate and offer a security technology at the pill level. This added layer of security is effective even when products are separated from the original package.

Table 3: General conclusions on overt features

Overt | Features	
Advantages	Disadvantages
User verifiable	Require user education to understood
Newer technologies more secure	May be easily mimicked
Can add decorative appeal	May add significant cost
Can be a deterrent to counterfeiters	May be reused or refilled
	May give false assurance

3. COVERT (Hidden) Features:

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The purpose of a covert features is to enable the brand owner to identify counterfeited product.

3.1 Invisible printing

Using special inks, invisible markings can be printed on almost any substrate, and which only appear under certain conditions, such as via UV or IR illumination. They can be formulated to show different colours with illumination at different wavelengths.

3.2 Embedded image

An invisible images can be embedded within the pack graphics which can only be viewed using a special filter, and cannot be reproduced by normal scanning means. The effects can be quite dramatic and well hidden.

3.3 Digital watermarks

Invisible data can be digitally encoded within graphics elements and verified by means of a reader and special software. The data can be captured using webcam, mobile phone or other scanning equipment, but the information is not visible to the human eye, and attempts to replicate it will be detected by virtue of the degradation of the embedded data.

3.4 Hidden marks and printing

Special marks and print may be applied in such a way that escapes attention and is not easy to copy. Their effectiveness relies on a combination of secrecy and subtlety, and hence no further details will be discussed here.

3.5 Anti –copy or Anti-scan design

Fine line background patterns appear as uniform tones, but when scanned or copied reveal a latentimages which was not previously visible. Commonly used on secure documents to prevent photocopying, the may be applied to product packaging as a background tint.

3.6 Laser coding

The application of batch variable details by laser coding requires special and expensive equipment, and results in recognisable artefacts which may be difficult to simulate laser codes can be applied to cartons and labels and plastic and metal components.

4. FORENSIC MARKERS

There is a wide range of high technology solutions which require laboratory testing or dedicated field test kits to scientifically prove authenticity. These are strictly a sub-set of covert technologies, but the difference lies in the scientific methodology require for authentication.

4.1 Biological taggants

A biological marker can be incorporated at extremely low levels (parts per million or lower) in product formulations or coatings, or invisible applied to packaging components. At such low levels they are undetectable by normal analytical methods, and require highly specific "lock and key" reagent kits to authenticate [12].

4.2 Micro taggants

Micro taggants are microscopic particles containing coded information to uniquely identify each variant by examination under a microscope. This may take the form of alphanumerical data depicted on small flakes or threads, or of fragments of multi-coloured, multi-layered laminates with a signature colour combination. These can be embedded into adhesives, or directly applied to packaging components as spots or threads.

Table 4: General conclusions on covert features

Covert Features	
Advantages	Disadvantages
Can be simple and low cost to implement	Need strict secrecy-"need to know"
Needs no regulatory approval	If widely known or used, may be easy to copy

Can be easily added to or modified	More secure options add supply complexity and cost

TAMPER-EVIDENT FEATURES]:

Tamper-evident packaging may involve container or primary pack systems or any combination thereof.

Note: Sealed paperboard cartons such as those sealed by gluing the end flaps and / or side-seam together are not an acceptable form of tamper-evident packaging [13].

i. Film wrappers – transparent

A transparent film with distinctive design is wrapped securely around the entire product container ensuring the product is completely sealed and a secure tight fit is achieved. The wrapper must be ripped or broken to gain access to the product [Figure 4].

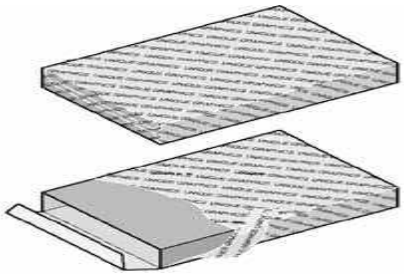

Figure 4: film wrappers

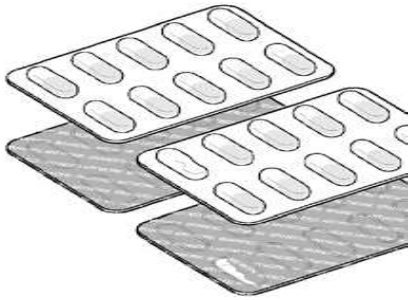

Figure 5: blister or strip packs

ii. Blister or strip packs

Individual doses (for example, capsules or tablets) are sealed in plastic and/or foil.

Blister or strip pack seals around individual compartments and the strip as a whole, must be intact and complete.

The individual compartment of the pack must be ripped or broken to gain access to the product.

The blister or strip pack materials cannot be separated or replaced without leaving visible evidence of entry [14] [Figure 5].

iii. Pouches, sachets and form fill seal packs:

The product is enclosed in an individual pouch or sachet that must be ripped, peeled open or broken to gain access to the product. The pouch or sachet must have a distinctive design.

Seals of the pouch or sachet cannot be separated and resealed without showing visible evidence of entry [Figure 6].

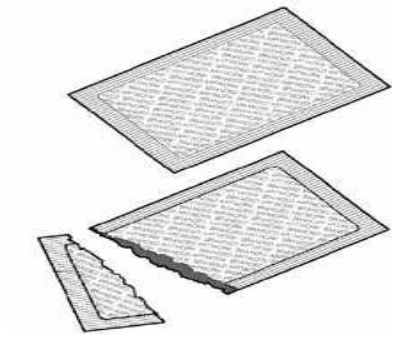

Figure 6: pouches, sachets

iv. Tape seals

Paper, foil or plastic with a distinctive design is sealed over all carton flaps or a container cap.

The seal or pack must be ripped or broken to gain access to the product.

The seals cannot be removed and reapplied, or the carton side-seam breached without showing visible evidence of entry [Figure 7].

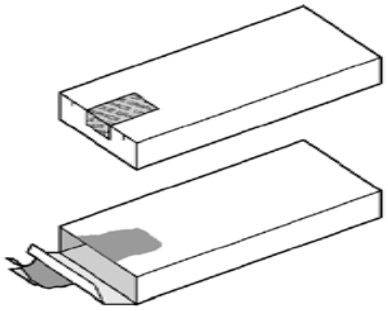

Figure 7: *Tape seals*

v. Bubble packs

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The product and container are sealed in a plastic bubble and mounted in or on a display card.

The plastic or card must be ripped or broken to gain access to the product.

The backing material cannot be separated from the bubble or replaced without leaving visible evidence or entry.

Bubble packs seals must be intact and completely sealed all the way around [Figure 8].

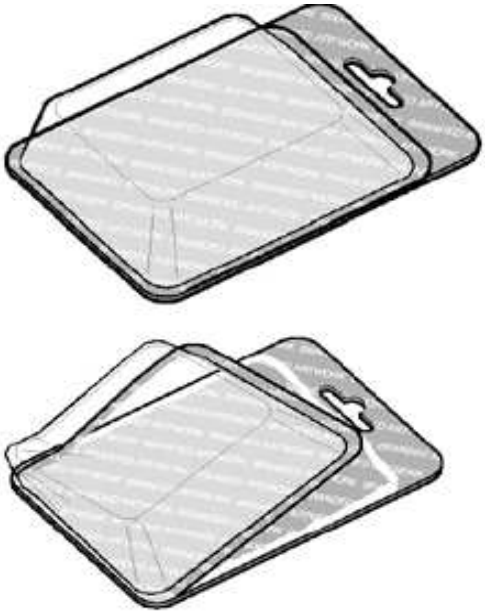

Figure 8: bubble packs

vi. HEAT SHRINK BANDS OR WRAPPERS

Bands or wrappers with a distinctive design are shrunk by heat to tightly seal the union of the cap and container.

The seal must be ripped or broken to gain access to the product. The wrapper cannot be removed and reapplied without visible damage [Figure 9].

Figure 9: heat shrink bands

vii. Container mouth inner seals

Paper, thermal plastic, polystyrene foam, plastic film, foil, or combinations thereof, with a distinctive design is sealed to the mouth of a container under the cap. The seal must be broken to open the container and gain access to the product. The seals cannot be removed without showing visible evidence of entry, and once removed, seals cannot be reapplied without showing visible evidence of entry [Figure 10].

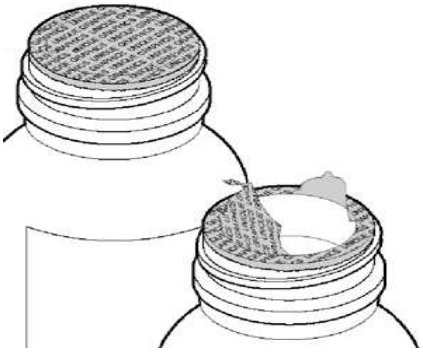

Figure 10: container mouth inner seals

viii. Breakable caps

The plastic or metal cap has a portion that breaks away on opening and remains on the neck of the container.

The cap cannot be removed or reapplied in its original state [Figure 11].

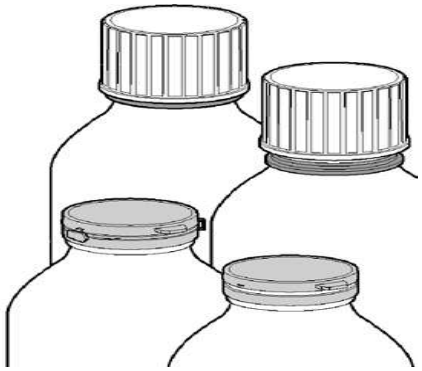

Figure 11: Breakable and tear-away caps

ix. Tear-away caps

The plastic or metal caps has a portion that is torn away in order to allow the remains on the

remainder of the cap to be removed to gain access to the product. The tear away portion must be clearly torn or missing once the package is opened. The cap cannot be removed or reapplied in its original state [Figure 11].

x. *Sealed metal tubes*

The lower end is sealed by folding or crimping.

That end must not be capable of being breached by unbending and refolding without visible evidence of entry.

The nozzle is blocked by seal or membrane. The nozzle seal must be broken or punctured to gain access to the product [Figure 12].

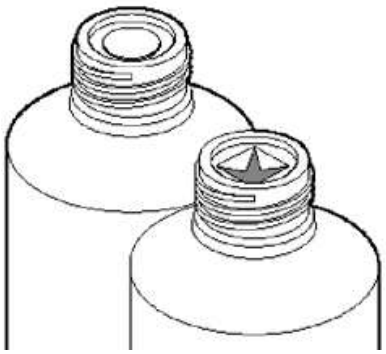

Figure 12: sealed metal tubes

xi. *Sealed plastic/ laminate tubes*

The lower end of the tubes is sealed by heat sealing and crimping. That end must not be capable of being breached without visible evidence of entry.

The nozzle is blocked by a seal, membrane or twist off top and must be broken or punctured to gain access to the product [16] [Figure 13].

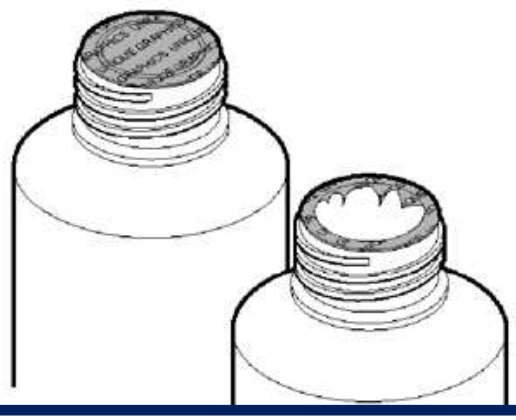

Figure 13: sealed plastic/ laminate tubes

xii. *Heat shrink bands or wrappers*

A band or wrapper is securely applied to a portion of the container, usually at the juncture of the cap and container. The band or wrapper is heat shrunk to provide a tight fit. The band or wrapper must be cut or torn to open the container and remove the product and cannot be worked off and reapplied without visible damage. The use of a perforated tear strip can enhance tamper-resistance. Cellulose wet shrink seals are not acceptable [17-20].

The knowledge to remove and reapply these seals without evidence of tampering is widespread.

The band or wrapper must employ an identifying characteristic that cannot be readily duplicated. An identifying characteristic that is proprietary and different for each product size is recommended.

Tinted bands or wrappers are no longer acceptable as an identifying characteristic because of the possibility that their material or a facsimile may be available to the public.

Conclusion:

To protect from counterfeit medicines patients have to check it. Now a day's pharmaceutical companies are using various anti counterfeit packaging as barcodes, holograms. There is chance to make duplicate copies of these packaging. Covert (invisible to naked eye) security features provide higher security compared to overt (visible) ones. Hence pharmaceutical companies may use modern anti counterfeit techniques as RFID to track and trace pharmaceutical products.

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20. Available at: http://a-cappp.msu.edu/sites/default/files/files/Spink_Tamper.pdf

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