Review Article

TAMPER EVIDENT PHARMACEUTICAL PACKAGING – NEEDS AND ADVANCES

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Accepted on: 24-02-2012; **Finalized on:** 20-03-2012.

ABSTRACT

Drugs need more care in their packaging than do most other products. Now a day's other than protection, presentation, identification, information and convenience; packaging must be tamper evident equally for primary and secondary packages. Tamper evident packaging having an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visual or audible evidence to consumer that tampering has occurred. After the Tylenol tragedy more emphasis has been given on control of tampering with different acts and regulation for the packaging. Different technological approaches are discussed in this work used to make product tamper evident. Also the smart packaging technology introduced with colour changing polymer, gas sensing dyes, bar coding. Great care is being taken for shipment by making pharma cargo tamper proof. With covert and overt technology, tamper evident packaging provide secure against counterfeiting attempts. But to reduce risk of tampering consumer education and GMP must be considered. With growing packaging demand in future all pharmaceuticals needs to be tamper evident.

Keywords: Tamper evident packaging, Tylenol tragedy, Counterfeiting, Covert and overt technology.

INTRODUCTION

One of the best general definitions of pharmaceutical packaging is "An economical means of providing protection, presentation, identification, information and convenience for a pharmaceutical product from the moment of production until it is used or administered.

Drugs need more care in their packaging than do most other products, because any failure in their packaging could result in changes in the drug that lead either to a failure to cure to illness to injury or even to death of the patient.[1]

Additionally modern packaging needs to be child resistant and tamper evident. Convenience, ease of use, hygiene package integrity and new dispensing methods must now also be provided for patient.

The FDA Rule requires the use of tamper-evident packaging on all over-the-counter drugs and some cosmetics. However, if a product in an adulterated form could harm a consumer, manufacturers have the responsibility of protecting the product and consumer against tampering, meaning that tamper-evident packaging transcends FDA regulations. No single feature is best for all products and all features can be violated in some manner, but effective tamper-evident features provide greater difficulty in doing so. Consumers should be aware of what to look for in tamper-evident packaging and pay attention to what product is being used[2].

Tamper-evident packaging may involve immediate-container/carton systems or any combination thereof. It is intended to provide a visual indication of package integrity when handled in a reasonable manner during manufacture, distribution and retail supply.

TAMPER-EVIDENT PACKAGING

Tamper evidence has been defined in the USA as the degree to which tampering is apparent to the observer.

Tamper – evident packaging therefore is packaging that makes tampering apparent to the observer, to some degree. In its definition of tamper resistant packaging, the US Food and Drug Administration (FDA) have made it clear that for their purpose, the observer is the consumer. This is an important point, because consumer observers are less knowledgeable than observers who design, specify, make fill packages. Consumer observer may misinterpret some of the sign of tampering that would be clear to those who make and fill packages. For this reason, FDA has stated that tamper-proof probably cannot be achieved. Now there is the question of how resistant or evident tampering is?

Tamper-resistant packaging is term originated by the Food and Drug Administration (FDA) in 1983, with the first publication of the regulation, requiring such packaging for OTC drugs sold at retail in the USA. The term was never widely accepted by packaging makers and users. They preferred 'tamper-evident'. The FDA has recently proposed to change its terminology to tamper-evident, based on the idea that the tamper-evident might emphasize to consumers that they should be looking for evidence of tampering rather than assuming without looking, that there has not been any tampering to a resistant package.

The regulatory requirement for tamper –evident packaging is directed against what is known as malicious tampering. It was not established with the intent to provide any control on casual tampering, or grazing, it is called reduction of successful malicious tampering is the goal.

There is another kind or level, of tampering to consider. It used to be called 'pilfering'. A product is stolen opened and the contents partially removed during transit; but target of the regulation is the malicious tamperer, working on retail packages

The package passes through number of stages, beginning with the container manufacturer, then to the product manufacturer, wholesaler, retailer, and, finally, Consideration of the life history and the functions of the package shows that five basic qualities are required – Protection, Identification, Presentation, Convenience, Economical[3]

Choice of packaging

The choice of packaging for any specific pharmaceutical product is dependent on the following principle factors

- ✓ The nature of product itself- its chemical activity, moisture sensitivity, effect oxygen and its compatibility with possible packaging materials
- ✓ The type of patient- e.g. Child, elderly adult, male or female, ethnic origin
- ✓ The form of the dose- free flowing granules, aqueous solution, cream, ointment, inhalation etc.
- ✓ Method and site of administering the medication- oral, topical, parenteral, ear, eye, nose, skin etc. whether a dispensing devices is to be used e.g. syringe, dropper etc.
- ✓ Method of distribution- Ethical through pharmacies and hospitals or OTC through retail outlets.
- ✓ Capacity of the packaging needed-small bulk pharmacies, OPD, unit dose etc.
- ✓ Required shelf life and likely sales areas.

Analysis of many stages in the life history of a package shows that hazards can be divided into two main groups- mechanical and environmental. The only exception is theft, which can be a serious risk with drugs and may demand special protection in certain cases.[1]

Major packaging types[4]

1- Primary and intermediate packaging.

2- Secondary packaging.

Definition

Tamper-Evident Packaging (TEP)**:**

Packaging having an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible or audible evidence to consumers that tampering has occurred.[1]

Tamper-evident packaging may involve immediate-container/carton systems or any combination thereof. It is intended to provide a visual indication of package integrity when handled in a reasonable manner during manufacture, distribution and retail supply. The visual indication is required to be accompanied by appropriate precautionary label statements to describe the tamper-evident feature(s) to the consumer and to warn that the absence of or damage to such feature(s) at the time of purchase is an indication of possible tampering with the product.

"Tamper proof" (as distinct from tamper-evident packaging) is not possible and, therefore, any suggestion that a package is tamper proof is considered to be deliberately misleading. [5]

Table 1: Typical primary package types for pharmaceuticals

Types of medication	Possible package types
Solid dose Oral liquids	Jars, tubes, blisters, strips, sachets, boxes cartons
Ear, Eye and nasal products	Bottles, unit dose pack
Throat product	Dropper bottles, squeeze and spray packs, unit and multi-dose systems
Parenterals -LVP -SVP	Glass and plastic bottles, pumps and aerosol sprays
Ointments ,creams, paste	Glass bottles, plastic bottles and plastic bags
	Glass or plastic ampoules and vials, Prefilled syringes
Special lung treatments	Glass, plastic and some metal containers, collapsible tubes (metal, plastic and laminated)
	Devices for administrating powders and liquids for inhalation, some glass but mostly plastics.

CONCEPTS

Tamper resistance: Difficult to compromise the contents of a package.

Tamper evidence: If the contents are compromised, it is clearly evident to the customer that tampering has occurred prior to use (absence of damage).

Tamper proof: It is considered as a 100% guarantee and therefore technically not feasible and therefore not realistic.

Counterfeit resistant packaging: a pharmaceutical packaging with a tamper evident or tamper resistant feature, overt and/or covert authentication features and track and trace feature in order to allow authentication of the individual packaging through the entire supply chain.

History of tamper–evident packaging

In 1975, the US FDA established a regulatory requirement for tamper indicating packaging to be used for ophthalmic preparations. The regulation specifies that the container for an ophthalmic preparation'…shall be so sealed that the contents cannot be used without destroying the seal'. In November 1982, the FDA issued regulation 21CFR211.132, tamper resistant packaging requirement for over-the-counter human drug products. The FDA compliance Policy Guide May 1992 describes several

technologies that the agency believes do satisfy the definition[1]

Tylenol case

November 1982, there was single occurrence of multiple malicious tampering of Tylenol packages in the city of Chicago took place, where seven people died from ingesting Tylenol capsules laced with cyanide. The Food and Drug Administration (FDA) reported 270 cases of suspected product tampering in the months following the Chicago poisoning cases in a wide range of products from pain relievers to eye drops to nasal sprays and even candy.

Malicious tampering is tampering with a packaged product with intent to do harm to individuals, known or unknown to the tamperer. Then 1991, another tampering incident resulted in two deaths and another person became severely ill. The product was capsule in blister package. It was believed that victims should have noticed the tampering and should have avoided using the product. Why they did not and how to address the issue became subject of FDA review.

In addition, on 18 January 1994 the agency took notable actions: first it proposed to change all its terminology from 'tamper-resistant' to 'tamper-evident'. The reason given is that this will change the focus from the assumption that there is a resistance to tampering the assumption that there is need to look for evidence of tampering. The second action was a request for comment from the public about whether or not there is need for some kind of performance standard for tamper-evident packaging. [1]

Types and effects of product tampering

Product tampering can be classified into five types:

• Criminal tampering**:**

An offender places one or more contaminated products on the shelf so that the consumers may purchase and consume the adulterated product without knowing.

• Staged tampering:

An offender contaminates a product to simulate that the manufacturer has been the victim of true tampering. An example is the Seattle case where staged tampering was used to cover a murder. This kind of tampering is also used in suicides to try to gain money for their family and cover the true manner of death.

• Extortion tampering:

An offender threatens to tamper with a product if their demands are not met. These demands are usually for substantial amount of money.

• Faked tampering:

Offenders alert the media, law enforcement, relevant manufacturers, or others of a non-existent tampering. Many of the alerts are merely hoaxes for entertainment.

• Suspected tampering:

Consumers alert the manufacturer when a package has been compromised, when a product appears unusual, or when they suffered particular symptoms after the consumption of the product. The consumer complaints usually refer to quality defects due to machinery failures rather than tampering. For example burns on package seals, packaging containing not the right quantity of the product, damage to the packaging caused by careless opening of cartons in retail stores. It has been reported that the number of complaints due to suspected tampering increase following a true case of tampering as the consumer anxiety is much higher.[6]

REGULATORY ASPECTS OF TAMPER–EVIDENT PACKAGING

Unusual sight, taste and smell usually alert the consumer to detect and identify a potential food tampering. But what happens when the tampering is not easily detectable, as is the case with OTC drug products?

To prevent future tampering and restore the public's shattered confidence in the products, the Food and Drug Administration and pharmaceutical manufacturers turned to the problem of securely packaging non-prescription drugs.

The Ad Council in the USA has developed some television public service shorts with simple message: "Before you tamper, know what you are in for- Five years!!!"

Anti-tampering regulations[6]

In the U.S. in 1983, as a result of the Chicago-area Tylenol poisonings, the Federal Anti-tampering Act (FATA) was passed.

The FATA outlaws:

- Tampering with any consumer product or its labeling or container
- Tainting any consumer product or rendering its labeling or container materially false or misleading with intent to cause serious injury to the business of any person
- Knowingly communicating false information that a consumer product has been tainted, if such tainting would create a risk of death or bodily injury to another person
- Knowingly threatening to tamper with a consumer product, its labeling or container
- Conspiring to tamper with a consumer product, its labeling or container

Less than a month after the Tylenol poisonings, the FDA enacted regulations that required manufacturers of the majority of over the counter drug products (OTC), some cosmetics and liquid oral hygiene products to package their products in tamper-resistant packages (TRP).

Tamper-resistant packaging requirement for OTC human drug products

a) General

The FDA has authority under the Federal Food, Drug and Cosmetic act to establish a uniform national requirement for tamper-resistant packaging (TRP) of OTC drug products that will improve the security of OTC drug products that will improve the security of the OTC drug packaging and help assure safety and effectiveness of OTC drug product

b**) Requirement for tamper-resistant packaging**

1) Each manufacturer and packer who packages an OTC drug product (except a dermatological dentifrices insulin, or throat lozenge product) for retail sale, shall package the product in tamper resistant package, if this product is accessible to the public while held for sale

To reduce the likelihood of successful tampering and to increase the likelihood that consumer would discover whether a product has been tamper with or not, the package is required to be distinctive by design e.g aerosol product container. By the use of one more indicators or barriers to entry that employ an identifying characteristic or by use of identifying characteristic (e.g. pattern, name, registered trademark, logo or picture)

A tamper resistant package involve an immediate container and closure system, or secondary container or carton system, or any combination of system intended to provide visual indication of packaging integrity. The tamper-resistant feature shall be designed to, and shall remain intact when handled in reasonable manner during manufacture, distribution and retail display.

2) Along with above feature any two piece hard gelatin capsule covered by this section must be sealed using an acceptable tamper-evident technology.[7]

c) Labeling

In order to alert consumers to the specific tamper-evident features used, each retail package of an OTC drug product covered by this section (except ammonia inhalant in crushable glass ampoules, containers of compressed medical oxygen, or aerosol products that depends upon power of liquefied or compressed gas to expel the contents from the container) is required to bear a statement and is prominently placed on the package.

Label should be so placed that it will be unaffected if the tamper evident feature of package is breached or missing.

If the tamper resistant feature chosen to meet the requirement in para (b) of above section is one that uses an identifying characteristic, then that characteristic is required to be referred in the labeling statement. For example, the labeling statement on a bottle with shrink band could say, "For your protection, this has an imprinted seal around the neck."

Table 2: Examples of label statements

Tamper evident feature	Suggested wording
Film Wrappers	Do not use if film wrapper is damaged or missing
Blister	Do not use if blister seal is broken
Strip Packs	Do not use if blister backing is damaged
Bubble Packs	Do not use if blister seal is broken
Heat Shrink Bands	Do not use if seal (around cap/under lid, etc.) is broken or missing
Wrappers	Do not use if tape (band) around cap is damaged Band around cap must be present to ensure package security. The seal over/around the cap is your assurance that the package has not been opened. For your protection, this bottle has an imprinted seal around the neck

d) Request for exemption from packaging and labeling requirement

A manufacture or packer may request an exemption from the packaging and labeling requirements of this section. A request for an exemption is required to be submitted in the form of citizen petition under this chapter.

e) OTC drug product subject to approved new drug application.

Holders of approved drug application for OTC drug products are required under this chapter to provide the agency with notification of changes in packaging and labeling to comply with requirement of this section[7]

cGMP regulations

Product tampering is not a new occurrence. However, as a direct result of several deaths in 1982 resulting from the malicious addition of cynide to Tylenol capsules, this section was introduced in to the cGMP regulations. The key elements of the regulation are:

1. It only applies to OTC products since these tend to be on open display with ready access to the public. It was considered that prescription products are maintained under control of the pharmacist and consequently are less vulnerable to tampering. The exemption of insulin was for the same reason. The other excluded categories-dentifrices, lozenges, and dermatological products-were considered to be less prone to potential tampering because of their inherent nature or use.
2. No test methodology or effectiveness criteria were established. It was considered that the development of these would be difficult, time-consuming, and probably highly controversial and would delay the introduction of tamper resistant packaging-which an apprehensive public needed in order to retain confidence in this essential form of medication (OTC). Use of tamper-resistant feature is on the secondary package allows the consumer to examine the product for possible tampering before purchase. This

obviously is a consumer benefit. However, any inadvertent damage to the feature during shipping or storage will result in refusal to purchase. Application to primary container, or a bottle mouth seal, will preclude this possibility.

3. Two-piece hard gelatin capsules have been most vulnerable to tampering. The regulation(the requirement was effective November 4,1999, while labeling changes had to be implemented by November 6, 2000) require two tamper resistant features, two halves sealed is considered to be one feature
4. Tamper resistant feature is to be "distinctive by design or by use of an identifying characteristic". An aerosol package is considered to be distinctive by design. This to preclude possibility of removal of the feature and replacement by commonly available material.
5. Labeling is to include specific reference to the tamper-resistant feature used and must be sufficiently explicit that malicious replacement can be identified by consumer. The tamper-evident statement must be prominently placed on the drug product package to alert consumers about the product tamper evident features.
6. Tamper-resistant packaging components are to be treated identically to other components (Compliance Policy Guide). Those coming in to direct contact with the drug product are subject to the container and closure provisions of cGMP regulation. Additionally, some tamper resistant features, such as neckbands, and breakable caps, may impact adversely on the ability to open the package with ease. Whereas majority of tamper resistance feature impart physical barrier to entry, it is anticipated that future developments will rely heavily on technologies, such as microencapsulated inks, which do not affect ease of opening.

Producers of OTC are required to use tamper-resistant packaging. If a company does not comply with the regulation, it could be subject to several penalties, including product seizure, injunction and criminal prosecution.

FDA regulations do not mandate a specific type of tamper resistant packaging. Manufacturers and packagers are free to use any packaging system as long as the tamper-resistant requirements in the regulation are met.[7]

Regulations in other countries

The regulation concerning TRP has been recently applied across other countries after the main standard was imposed by the U.S. authority.[6]

Australia

In June 2003, The Therapeutic Goods Administration published, on behalf of the Industry Government Crisis Management Committee, the Code of Practice for the Tamper-Evident Packaging (TEP) of Therapeutic Goods (Edition 1). "Although the Code is not currently mandatory the Australian therapeutic goods industry is encouraged to continue to comply with the Code of Practice on a voluntary basis in anticipation of it becoming a mandatory standard The Code of Practice was developed to reflect the world's best practice in the TEP of therapeutic goods, with the intention that it be regularly reviewed and amended as appropriate to accommodate packaging innovations and new information on packaging performance" There are no significant deviations from the FDA regulation.

Europe

In a number of European countries, it is possible to sell OTC products in supermarkets without any further supervision. These countries include the United Kingdom, Holland, Switzerland, Ireland, Norway, Denmark and Austria. In other countries, such as Italy, Portugal and Spain, the regulations require a pharmacist nearby along with a dedicated pharmacy department. Since the selling of medicinal products directly on the store shelf is still a relatively new concept in these countries. There are currently no "specific" significant regulations like those in the U.S. in force.

A consumer or his family can file a civil suit demanding compensation from the manufacturers if a tampered product results in injury or death.

VARIOUS TECHNOLOGIES OF MAKING A PACKAGE TAMPER-EVIDENT

Most container closure systems which are used today either as primary or secondary packaging for pharmaceutical packages, such as bottles for solid dosage forms and liquids, vials for parenteral dosage forms such as lyophilisates, powders or liquids, tubes for semisolids and are available with special features to prove whether the packaging has been opened previously. The packaging technologies listed below are considered to meet the requirements for TEP provided that they are properly designed and appropriately used. Whilst these classes of packaging are acceptable, they should not be seen to be exclusive of other packaging types or to preclude technological innovation. Tamper-evident packaging must not be regarded as replacing or obviating the need for Child Resistant Closures wherever the law requires such closures. In selecting/developing tamper-evident packaging, manufacturers are urged to give serious consideration to the needs of arthritic or manually impaired persons

Knowing whether a package has been tampered which is equally important to consumers. The main purposes in lowering the risks of tampering are first to eliminate tampering and secondly to locate the already tempered products on the shelf by identification.[8]

Folding boxes

For folding boxes there are tamper evident security seals and tapes that destruct themselves while removing or seals with void effect. There are also folding boxes itself inherently evident by their principle of construction, by additional panel with perforation and option to close the box after first opening. There are also glued boxes with no option to close after first opening. For practical reasons, tamper evidence should be concentrated on the part of the packaging which is also serving for authentication purposes. In most cases it is assumed that this will be the folding box.[9]

Figure 1: Folding Boxes

Induction cup sealing technology,

Conventional bore sealing has been the most widely used method of sealing containers as it is inexpensive and easy to manufacture. Bore seals however do not form hermetic, flexible or even reliable seals as they leak.

Induction Cup sealing technology making it possible to now creates airtight, hermetic seals on the neck of the container. The seal is strong, flexible yet easy to remove and provides protection against cross contamination and an effective tamper-evident layer. The process can also produce significant cost saving.

The process of Induction Cup Sealing is based on the principle that a conductive material like aluminum foil heats up on exposure to high frequency magnetic field generated by an Induction Unit. This is a non-contact process without direct heat transfer. Due to this, the sealable closure liner can be placed in the cap by the manufacturer prior to sealing. The Induction Sealing process can be very easily incorporated on any existing filling lines from manual filling to the fully automated filling and capping lines. The Induction unit can have its own conveyor or can be mounted on the existing conveyor line. Separate operation of sealing foil and lid assembly are no longer required.

Figure 2: Induction cup sealed container

Induction Sealing can be used with almost any type of cap or container to provide a tight bond suitable with Foods, Beverages, Oil & Lubricants, Drugs, Chemicals, Pesticides, and Pharmaceuticals etc.

Induction wads:

The wad basically consists of four layers

- ✓ Cardboard or Foam Packing
- ✓ Wax Layer
- ✓ Aluminum Foil
- ✓ Sealing Film

The line of force radiates through the foil and induces current flow in it. This increases the temperature of the foil. Due to this the sealing film melts and adheres to the lip of the container. After the seal is broken, the board or foam packing is retained by the cap. Wads for HDPE, LDPE, PET and PP in different thickness are easily available

Advantages:

• Tamper proof

• Keeps products fresh

• Protects against Leakage, Oxidation and Contamination
• Helps in sales promotion as the foil on the inside can also be used for advertising or promotional purposes
• Maximum filling speeds with minimum effort
• Indirect heating allows heat sensitive products to be sealed faster and safely

Figure 3: Induction Wads

Film wrappers

A transparent film with distinctive design is wrapped securely around the entire product container. The film must be cut or torn to remove the product. The wrapper must have an identifying characteristic (e.g. a pattern, name, registered trade mark, logo, or picture) that cannot be readily duplicated. Tinted wrappers are not acceptable as an identifying characteristic because of the possibility that their material may be available to the public. A reasonably tight "fit" of the film around the container must be achieved, e.g. by a heat shrink type process.

Figure 4: Stretch film wrapping

Sealing of a film wrapper with overlapping end flaps is acceptable only if the ends cannot be opened and resealed without leaving visible evidence of tampering. The use of cellophane with overlapping end flaps is not acceptable because of the possibility that the ends can be opened and resealed without leaving visible evidence that tampering has occurred.

Although film can be accomplished in several ways and varies in configuration from packaging equipment to packaging equipment, it can be generally categorized in to following types[10]

End-folded wrapper

Fin seal wrapper

Shrink wrapper

End-folded wrapper

This wrapper is formed by pushing the product in to sheet of overlapping film, which forms the film around the product and fold the edges in gift wrap fashion. Film used must be heat-sealable on both surfaces. Materials commonly used for these applications are cellophane and polypropylene.

To be tamper-resistant, the overwrap must be well sealed must be printed or uniquely decorated to exclude the possibility of having an alternate overwrap substituted in its place. The printed surface of the carton being wrapped may also be coated with heat sensitive varnish, which causes overwrap to bond permanently to the paperboard carton during sealing of overwrap. The removal of the overwrap would deface the carton, making the carton unsuitable for reuse.[10]

Fin seal wrapper**:**

These seals are formed by crimping the film together and sealing together the two inside surfaces of the film, producing a "fin" seal. The overwrap can be removed or opened only by tearing the wrapper.

Shrink wrapper:

The shrink wrap concept involves the packaging of a product in thermoplastic film that has been stretched and oriented during its manufacture and that has the property of reverting back to its unstretched dimensions as the film unwinds on the overwrapping machine, a pocket is formed in the fold of the sheet, in to which the product is inserted. An L shaped sealer seals the remainder of overwrap and trims off the excess film. The loosely wrapped product is then moved through heated tunnel which shrinks the overwrap in to a tightly wrapped unit.

Figure 5: Shrink wrapper

Blister or strip packs

It is a packaging configuration capable of providing excellent environmental protection, coupled with an esthetically pleasing an efficacious appearance .it also provides user functionality in terms of convenience, child resistance, and now temper resistance.

The blister package is formed by heat-softening a sheet of thermoplastic resin and vacuum drawing the softened sheet of plastic in to a contoured mold. After cooling, the sheet is released from the mold and proceeds to the filling station of the packaging machine. The semi-rigid blister previously formed is filled with product and lidded with a heat-sealable backing material. The backing material, or lidding, can be of either a push through or peelable type. The use of peelable backing materials for blister packaging must be carefully evaluated to ensure that peel strengths are sufficient to meet tamper-resistance objectives.

Dosage units (for example, capsules or tablets) are individually sealed in plastic or foil. The individual compartment must be torn or broken to obtain the product. The backing materials cannot be readily separated from the blisters or easily replaced without leaving evidence of tampering.

Strip package

A strip package is a form of unit dose packaging of tablet or capsules. A strip package is formed by feeding two webs of heat sealable flexible film through either a heated crimping roller or a heated reciprocating platen. The product is dropped into the pocket formed prior to forming the final set of seals. Since the sealing is usually accomplished between pressure rollers, a high degree of seal integrity is possible.

Bubble packs

The bubble pack can be made in several ways but is usually formed by sandwiching the product between a thermoformable, extensible, or heat-shrinkable plastic film and a rigid backing material, this is passed through a heated tunnel, which shrinks the film into bubble or skin over the product, firmly attaching it to the backing card.[5]

Figure 6: Bubble pack

The product and container are sealed in plastic and mounted in or on a display card. The plastic must be torn or broken to remove the product. The backing material cannot be readily separated from the bubble or easily replaced without leaving evidence of tampering.

Heat shrink bands or wrappers

The shrink band concept makes use of the heat-shrinking characteristic of a stretch oriented polymer usually PVC. The polymer is manufactured as an extruded, oriented tube in a diameter slightly larger than the cap and neck ring of the bottle to be sealed. Bands or wrappers with a distinctive design (e.g., a pattern, name, registered trade mark, logo, or picture) are shrunk by heat to seal the union of the cap and container. The seal must be cut or torn to remove the product. The band or wrapper cannot easily be worked off and reapplied without visible damage to the band. Use of a perforated tear strip can enhance tamper evidence. Cellulose wet shrink seals are not acceptable as the knowledge of how to remove and reapply these seals without evidence of tampering is widespread.

Figure 7: Heat shrink band

Foil, paper, or plastic pouches

The flexible pouch is packaging concept capable of providing not only a package that is tamper resistant, but also, by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling, sealing (f/f/s) equipment.

The product is enclosed in an individual pouch that must be torn or broken to obtain the product. The pouch should have a distinctive design (e.g., a pattern, name, registered trademark, logo, or picture).The end seals of the pouches cannot be separated and resealed without showing visible evidence of entry.

Figure 8: FFS ampoules

For sterile medical devices, packaging is designed so that it cannot be opened without obviously damaging the unit pack or seal of the unit pack, which is non resealable and carries a label statement "Sterile if in unopened undamaged pack" or words or symbols to that effect. This type of packaging is considered to be tamper-evident without additional labeling requirements. Direct printing of the label on the container is preferred to using a label that could be removed and substituted.

Bottle mouth inner seals

A bottle may be made tamper-resistant by bonding an inner seal to the rim of the bottle in such a way that access to the product can only be attained by irreparable destroying the seal

Various inner seal compositions may be used like

- ✓ Glassine and foil laminations.
- ✓ Glue mounted.
- ✓ Pressure sensitive adhesive.
- ✓ Heat sensitive adhesive.

Paper, thermal plastic, polystyrene foam (except those applied with pressure sensitive adhesive), plastic film, foil, or combinations thereof, with a distinctive design (e.g., a pattern, name, registered trademark, logo or picture) is sealed to the mouth of a container under the cap. The seal must be torn or broken to open the container and remove the product. Seals applied by heat induction to containers appear to offer a higher degree of tamper evidence than those that depend on an adhesive to create the bond.

To meet tamper-resistant criteria, the inner seal must be printed or decorated with unique design. The seal must also be bonded sufficiently to ensure that its removal would result in destruction of the seal.

Tape seals

Tape involves the application of a glued or pressure sensitive tape or label around or over the closure of the package, which must be destroyed to gain access to the packaged product. The paper used most often is high density lightweight papers with poor tear strength. Paper or foil with a distinctive design is sealed over all carton flaps or a bottle cap. The seal must be torn or broken to remove the product Tape seals are acceptable only if they contain a unique feature that makes it apparent if the seals have been removed and reapplied, e.g., a permanent adhesive.

Breakable caps

Breakable closures come in many different designs. The roll on cap design used in the past for carbonated beverages uses an aluminum sheet, which placed over bottle neck during capping operation. The cap blank is held on the bottle under pressure while rollers crimp and contour the bottle tread into the cap blank. The bottom portion of cap is rolled around and under the locking ring on the bottle neck finish. This lower portion of the cap blank is usually perforated so that it breaks away when the cap is unscrewed, which serves as visible sign of prior opening.

A ratchet-style plastic cap is also commonly used for a number of different products. In this design the bottom portion of closure has a tear-away strip, which engages a ratchet on the bottle neck. To remove the closure, the

bottom portion of the closure must be torn away to disengage the ratchet and allow the removal of the cap.

The container is sealed by a plastic or metal cap that either breaks away completely when removed from the container or leaves part of the cap attached to the container. The cap, or a portion thereof, must be broken in order to open the container and remove the product. The cap cannot be reapplied in its original state.

Figure 9: Heavy screw cap with tamper evident tear-off locking flange

Sealed metal tubes or plastic blind-end heat sealed tubes

Collapsible tubes used for packaging are constructed of metal, plastic, or lamination of foil, paper, and plastic. Metal tubes are still used for those products that require high degree of barrier protection afforded by metal. Puncture inserts, which are usually made of aluminum 3 to 5 mil thick, are used to seal the tube opening for tamper resistance.

Both ends of the tube are sealed. The mouth or blind-end must be punctured to obtain the product. A tube with a crimped end is acceptable if the crimped end cannot be breached by unfolding and refolding without showing visible evidence of tampering. Direct printing of the label on the container is preferred to using a label that could be removed and substituted.

Cans (both all-metal and composite)

The top and bottom of a composite can must be joined to the can walls in such a manner that they cannot be pulled apart and reassembled without visible evidence of entry. Rather than attaching a separate label, direct printing of the label onto the can (e.g., lithographing) is preferred.

Figure 10: Metal cans

Cardboard cartons

Folding paperboard cartons have been used as secondary package for OTC products for many years. Seal end cartons uses externally applied glue or hot melt to provide carton sealing. Cardboard Cartons specifically designed to ensure that in order to obtain the product, the carton seal must be cut or must be non-resealable without showing visible evidence of en torn to remove the product and must not be able to be easily worked open and resealed without obvious damage to the carton.[5]

Capsule sealing technologies

Technologies for sealing two piece hard gelatin capsules are available that provide evidence if the capsules have been tampered with after filing. Such sealing technologies currently in use include sonic welding, banding and sealing techniques employing solvents and /or low temperature heating. These examples are not intended to rule out development and use of other capsule sealing technologies. Manufacturers may consult with FDA if they are considering alternative capsule sealing processes.[1]

As mentioned above, some manufacturers make tamper-evident capsules by sealing the joint between the two capsule parts. Sealing them with colour gelatin band makes it distinctive looking. If removed band cannot be restored. Capsule may also be sealed through a heat welding process that fuses the capsule cap to the body through the double wall thickness at their juncture. The process result in distinctive ring around the capsule where heat welded

Still another process uses a liquid wetting agent that lowers the melting point in the contact areas of the capsules cap and body and thermally bonds the two parts using low temperature (40-45°C). Capsules may be sealed by lightly coating the inner surface of the cap with a warm gelatin solution immediately prior to placement on the filled capsule body.[11]

In-built tamper-evident controls

Products such as In-Vitro Diagnostics (IVDs), which are supplied direct to the public, may have built in controls which demonstrate clearly that the product is unacceptable by showing a test-method failure, avoiding the potential for false results. Products incorporating such controls, which must be obvious to the user from the packaging information / instructions when trying to assess the test results, are considered as having Tamper-evident controls, and for the purposes of this Guideline are considered to comply with the requirements without needing additional packaging or labeling.

Aerosol containers

Pressurized aerosol containers are believed to be inherently tamper-resistant because of their particular design. However it is recommended that a secure over cap be used. Direct printing of the label on the container (e.g., lithographing), is preferred to using a paper label which could be removed and substituted.

Figure 11: Aerosol Design

SMART PACKAGING TECHNOLOGIES

It is based on optically variable films or gas sensing dyes, involving irreversible colour changes, it is becoming more widespread and cost-effective for disposable packaging of modity items.

Piezoelectric polymeric materials might be incorporated into package construction so that the package changes colour at certain stress threshold. In this way, self-bruising closure on a bottle or jar might indicate that attempts had been made to open it.

The new packaging is natural red to light-pink colour. When punctured light and air react with packaging in a process called photochemical oxidation, which forms a type bruising. This form of smart packaging that indicates when the integrity of the barrier has been breached.[8]

Two dimensional bar-coding

Market available tamper evident packages can be imprinted with a product and item specific barcode to make the package traceable through the supply chain. If the itemized barcode is based on a large set of randomized numbers, it is nearly impossible for the counterfeiter to generate legitimate codes to be used on a counterfeited package. On the other hand this allows the authentication of the package at any point in the supply chain

Make Pharma cargo tamper-proof

Pharma company has developed a security system to protect cargo containers and pallets from theft and tampering. Manchester UK-based Tamper Proof Container Systems (UK) Ltd -says that the system can detect all intrusion attempts on all six sides of a container instantly and transmit an alarm to the shipment owner in real time, helping to guard against not only theft but also deliberate adulteration of cargo. The technology comprises a four-layer security 'skin' which is sprayed onto the interior of a shipping container or other storage unit. Incorporated into the skin is a fine copper wire mesh embedded in a protective polymer which creates a circuit. Any attempt to gain entry to the container - by forcing the door or drilling a hole into it - breaks the circuit and detects the intrusion. An alert is sent to the cargo owner or shipper using built-in GSM/GPRS or satellite antennae via a centralized device management centre (DMC).

The US Department of Homeland Security is very interested in identifying technologies that can detect intrusion as part of its anti-bioterrorism programme, while other applications include prevention of drug smuggling, theft of intellectual property and human trafficking.

The system is extremely reliable, with a false-positive rate of zero due to the robust protection afforded by the fire-retardant polymer coating. When an intrusion is detected the affected circuit is removed and a replacement sprayed into place.[12]

Unacceptable tamper-evident features

Sealed Cartons

Sealed paperboard cartons as currently available in the marketplace (e.g., cartons sealed by gluing the end flaps together) are unacceptable. However, future technological advances may provide sealed paperboard packages that meet the intent of the TEP requirements.

Paper, thermal plastic, polystyrene foam bottle seals applied with pressure sensitive adhesive do not offer adequate evidence of tampering. Cellulose wet shrink seals are not acceptable as the knowledge of how to remove and reapply these seals without evidence of tampering is widespread.

Tape seals that do not carry a feature that makes it apparent if the seals have been removed and reapplied, e.g., a permanent adhesive are unacceptable.

Anti-counterfeiting measure

The force aims to create a comprehensive system of modern protective measures against counterfeit drugs. One of the measures is to ensure the security of packaging by using tamper resistant tapes, holograms and colour-shifting inks and dyes.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) have published a white paper4 on the anti-counterfeiting of medicines. It is clearly stated in the document that packaging should be adequately marked to prevent reproduction. In cases of tamper-proof packaging that needs to be repackaged, the authorized repacker shall repack again in a tamper-proof packaging.

New secure packaging technologies have been developed to facilitate easy regulatory compliance. Defeating the counterfeiters demands a multi-level approach, an element of which is secure packaging. However, in order to ensure optimal security of pharmaceutical packaging, both overt and covert technologies need to be used.

The solutions incorporate sophisticated covert technology for use by customs agencies, authorized distributors and other parties with access to high tech readers or secure databases. They also feature advanced overt identification capabilities for users who have to rely on the evidence of their own eyes.[13]

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.

- *Holography*
- *Colour Shift Inks*

Covert Technologies

The level of packaging security can be further increased with the introduction of covert and forensic features. Covert techniques such as infra red (IR) and ultra violet (UV) pigments, micro text and microscopic tagging are invisible and difficult to detect and replicate without specialist detection equipment. As a result, they provide a higher level of protection. Forensic solutions include molecular markers and biological tracers. These features can only be identified using laboratory equipment, offering complete confidence in packaging authentication.

- *UV Inks and Print*
- *Colour and UV Micro text Print*.
- *Taggant Authentication*

Combining Overt and Covert Technologies

Security Design and Print

Security print techniques using highly defined print lines to create complex designs that are difficult to originate and print are also highly effective in the fight against counterfeiting. Sophisticated overt and covert security design features, created using the latest software, can be built into each design, protecting pharmaceutical packaging from counterfeit. These include engraved images, relief images, warp grids, variable line width, guilloche designs, crystal patterns and special rasters.

Security Tear Tape

Security tear tape in combination with shrink sleeves as an anti-tamper solution around bottle caps can be used. The tear tape is an ideal medium to integrate a brand protection solution into product packaging. It can carry a variety of sophisticated brand protection features available from overt and covert authentication and tamper evidence technologies.

The tear tape technology provides solutions for authentication, tamper evidence and product coding. It is virtually impossible to remove the tear tape without destroying it, thereby preventing opening packs, refilling and resealing them without detection. In addition, the removal of the tear tape from the original packaging can be designed to damage the pack surface, leaving behind a void/ tampered message on the pack.

REDUCING THE RISK OF PRODUCT TAMPERING

No single solution can be considered as "tamper proof". Often multiple levels of security need to be addressed to reduce the risk of tampering. Some considerations might include:

- Identify who a potential tamperer might be: average user, child, psychopath, misguided joker, saboteur, organized criminals, and terrorists. What level of knowledge, materials, tools, etc. might they have?
- Identify all feasible methods of unauthorized access into a product, package, or system. In addition to the primary means of entry, also consider secondary or "back door" methods.
- Control or limit access to products or systems of interest.
- Improve the tamper resistance to make tampering more difficult, time-consuming, etc.
- Add tamper-evident features to help indicate the existence of tampering.
- Educate people to watch for evidence of tampering.

In order to prevent and reduce the risk of tampering following industry level points should also be considered:[6]

- ✓ Implement Good Manufacturing Practice (GMP)
- ✓ Apply appropriate tamper-evident packaging consistent with regulations and product use.
- ✓ Reinforce and provide an effective product recall strategy.
- ✓ Apply the right strategy in case of tampering in respect of media and communication.

Appropriate tamper-evident packaging

What is crucial and can point out the effectiveness of a package is its ability to resist violation and the difficulty that a potential tamperer encounters in trying to restore the package to its original condition. The only way to enhance its effectiveness is during the package design phase. At this point various tests can be carried out to verify the quality of the packaging against tampering and highlight its possible weaknesses. The design and product development is a very important element for product liability prevention as deficiencies can easily be corrected at this stage.

Large sections of the population encounter difficulty in opening consumer packaging of many kinds. Screw-caps in particular can cause problems for a range of people with a variety of impairments. Testing of a novel multi-axial force and torque transducer are carried out, designed for the study of loading conditions when tamper-evident bottle closures are opened manually. Result of these tests shows that elderly and young groups exhibit significantly different torque and force profiles to open bottles. It is anticipated that the transducer will be a valuable tool in future studies of opening strategies.[14]

Products recall strategy

In cases of tampering, it is very important to act promptly. J&J was able to recover from the Tylenol poisonings quickly due to its successful product recall strategy. The chemical/pharmaceutical company recalled the capsules within days (the recall included approximately 31 million bottles, with a retail value of more than 100 million dollars) and subsequently introduced tamper-resistant

tablets shaped like capsules within months (coupled with significant price promotions), which set a standard for the industry. Whereas at the time of the scare the market share of Tylenol collapsed from 35 to 8 percent, it recovered in less than a year, thanks to J&J's prompt and aggressive reaction[6]

As in most cases, the easiest way to respond promptly is to plan ahead. Every company should have a recall plan which provides information on "who" "what" "where" and "how". Failure to prepare adequately for a product safety recall can result in considerable and permanent damage to a company's brand and reputation. Although a company may recall their product for a variety of reasons, the recall due to tampering is very critical for an industry and needs to pay special attention.

Future Packaging

In the recent past there has been a growing demand for novel packaging methods for the fast growing pharmaceutical industry. Pharmaceutical packaging demands high standards such as, user safety, preservation, hygiene, packaging differentiation and efficiency. Chemical resistance, transparency and toughness of packaging enhance safety and efficiency of the drugs.

World pharmaceutical packaging demand is forecast to rise 5.9 percent annually to over $34 billion in 2011. Western Europe, the US and Japan will absorb nearly three-fourths of this amount due to the presence of the most advanced drug producing sectors. The US will remain the largest consumer of pharmaceutical packaging as new sophisticated therapies with specialized packaging needs are introduced[15]

The chart illustrates percent revenue shared between the various applications in the US pharmaceutical packaging market.

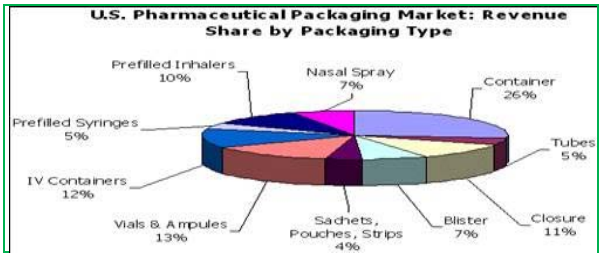

Figure 12: Packaging Market *[Source: Frost & Sullivan]*

In a global pharmaceutical market the USA and Europe have been familiar with the use of tamper proof and child resistant packaging for many years. However, there still are regions where the need is only just emerging. In addition to this, there is an overall drive for sustainability in packaging where pharmaceutical products are not immune [16].

Global market growth for pharmaceutical closures and accessories will be led by child-resistant, senior-friendly and dispensing closures; compliance-enhanced prescription containers; high visibility labels; and tamper-evident and anti counterfeit accessories. Demand for these products will benefit from stricter government and industry standards covering the safety, security and ease of use features of drug containers.[17]

Figure 13: Sensor based packaging quality control

In the year 2020 almost 16% of the population will be over 65 year old. The question of elderly acess has been raised. Both the regulatory and the industrial communities must address the needs of senior citizens as well those of the handicapped. This has led to the importance of providing tailored packaging solutions, which assures the effectiveness of the drug.[18]

CONCLUSION

It is certain that the achievement of tamperproof package is not possible, under currently foreseeable and commercially viable circumstances, there is no doubt that tamper-evident packaging can be achieved but this involves customer education. Packaging which incorporates a degree of tamper resistance is also possible if combined with better security arrangement, but is likely to be costly. Even if original pack dispensing for medicines were eliminated, the determined malicious tamperer could still cause problem. Education in recognizing the signs of tampering is probably the best bet.

Today the risk of tampering is foreseeable. This risk can be minimized if specific precautions are followed in design and manufacturing and consumers are properly educated by proper labeling.

Currently the likelihood of tampering is low, but the severity of its consequences, should tampering occur, is very high. Companies may suffer significant and irreparable damage to their brand and reputation if their product is tampered with and they are found unprepared to deal with an eventual crisis. With adequate precautions, planning and preparation, manufacturers will be able to reduce any potential damage to themselves and their consumers.

Anti-theft, tamper evidence and authentication solutions enable inferior and potentially harmful counterfeit products to be reliably intercepted and stolen genuine products can be recovered. By implementing the new security techniques, robust and reliable protection from tampering, copying and brand infringement is enabled and counterfeiting becomes a difficult and costly process.

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