

Compliance for EU Standards Tamper-Evident Pharmaceutical Packaging

How to ensure tamper-evident pharmaceutical packaging to comply with EU directive 2011/62/EU and EN 16679

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Introduction

Falsified medicines are fake medicines that pass themselves off as real, authorized medicines. They may contain ineffective or incorrect doses of active ingredients and pose a major threat to public health and safety.

As falsifications become more sophisticated, the risk of falsified medicines reaching patients in the EU increases every year. Not only do falsified medicines present an incalculable health risk for patients, they also damage the corporate image of pharmaceutical manufacturers and can lead to large financial losses.

To control the increasing number of falsified products in the European Union, in 2011 the EU adopted Directive 2011/62/EU entitled "Directive for prevention of the entry into the legal supply chain of falsified medicinal products", or in short "Falsified Medicines Directive". The Directive requires all EU Member States to implement a system to protect consumers from falsified medicines by February 9, 2019 at the latest. Failure to comply will result in pharmaceutical companies being unable to supply their products.

The Directive requires the outer packaging of any medicine to be provided with:

- Security features which make it possible for wholesalers and persons who are empowered or authorized to dispense medicines to the public to verify the authenticity of the medicine and to identify single packs.
- A device which makes it possible to check if the outer packaging has been tampered with.

This white paper focuses on point two – tamper verification features for medicinal product packaging, and looks at solutions which can help pharmaceutical manufacturers and packaging companies meet requirements specified in European Standard EN 16679.

The EU's Falsified Medicines Directive

In 2011, the European Parliament and the Council of the European Union enacted Directive 2011/62/EU. The Directive aims to prevent falsified medicines from entering the legitimate supply chain by adding features to the packaging that allow pharmacists and supply chain professionals to verify the authenticity of each individual pack. It is also intended to harmonize safety features for medicinal products within the Union.

From February 9, 2019, every prescribed drug placed on the EU market must be labelled with a 2D datamatrix code containing a unique serial number and more to enable it to be verified. The Directive also stipulates measures to verify the integrity of packaging. One stipulation is that on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging shall appear, among others, "a device allowing verification of whether the outer packaging has been tampered with".

The Directive does not, however, specify any details of tamper evidence, which is why various industry players, as part of a stakeholder model, sat together to develop European Standard EN 16679 "Packaging – Tamper Verification Features for Medicinal Product Packaging". Published in March 2015, the Standard specifies requirements and provides guidance for the application, use and check of tamper verification features to the packaging of medicinal products. The European Standard only becomes effective with publication of Directive 2011/62/EU, and medicines placed on the market which incorporate tamper verification features in accordance with EN 16679 will meet the requirements of Directive 2011/62/EU.

In-depth information about "serialization" – the process of printing and verifying unique serial numbers on medicines can be found in a separate METTLER TOLEDO white paper entitled "Serialization of Pharmaceuticals".

For further information visit www.mt.com/pce

What Does Tamper Evidence Mean?

Tamper evidence is the term used for a feature that makes unauthorized access to a product easily detectable. Tamper evidence should not be confused with tamper resistant, which is a packaging attribute intended to make access to a product more difficult. Although unlawful access to a medicinal product cannot be prevented, the aim of tamper evidence is to ensure that the packaging is at least damaged enough when opened to allow manipulation to be detected.

A tamper-evident package, according to the regulations of the Food and Drug Administration (21 CFR § 211.132), "is one having one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred."

Tamper verification features ensure that any illicit opening of the outer packaging during the supply chain, for example to replace a product's contents, is immediately apparent.

Ensure EU Compliance

A number of tamper-evident solutions exist which can help pharmaceutical manufacturers and packaging companies comply with the EU's Falsified Medicines Directive. The four main solutions outlined in EN 16679 are:

- Gluing
- Special folding techniques
- Film wraps, and
- Adhesive seals

Let us now look at each solution in turn.

2 Gluing

Gluing folding boxes is a common technique used to seal packaging. However, in the future gluing will double up as a security feature as packaging must be incapable of being opened at gluing points without manipulation being apparent.

A solidified glue layer between two cardboard areas with dispersion glues cannot be separated without damaging the fibers of the cardboard surface. Manipulating a glued point is difficult because solidified cold glue cannot be restored to its original state, even by adding water or other substances. After a box is opened by manipulation and reglued, the packaging will no longer be flat in the glued area.

Two advantages of gluing are that it is one of the most economical sealing solutions and causes very little loss of process speed. Furthermore, gluing machines can be integrated into existing production and packaging lines without incurring large costs. However, cold glue can take a long time to set. In contrast, hot melts set very quickly and hold an object in place, but are not always tamper-proof. Hot melts can be reversibly softened by adding heat and hardened again by reducing the temperature. A hot melt glue point can therefore be easily opened and manipulated without detection.

The ideal solution to comply with the tamper-evidence regulations is to use a combination of hot melt and cold glue. The hot melt enables a spontaneous bond to be made and will set quickly and hold the object in place, while the cold glue will provide a permanent, tamper-evident seal after filling. Manipulation by means of heating or spontaneous cooling, to which the hot melt reacts critically, is not possible with combination gluing once the cold glue has set. However, folding box structures that prevent the cold glue from being smeared or removed in the packing line must be used.

Advantages

- Proven and common technology.
- Economical sealing solution.
- Little loss of process speed.

Disadvantages

- Cold glue takes a long time to set.
- Hot glues are not always tamper-proof.



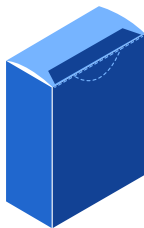
a) Original condition



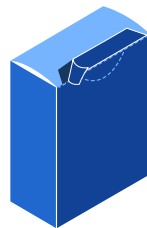
b) Where the opening of the box has been tried



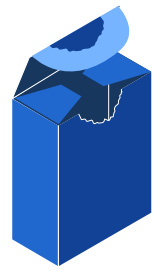
c) Opened

Figure 1: Example of a folding box closed with glue

a) Original condition



b) Where the opening of the box has been tried



c) Opened

Figure 2: Example of a folding box with perforations closed with glue

3 Special Folding Techniques

Using a specially-constructed folding box is another option to meet the EU regulations. The flaps and body of this type of box are designed to activate the security feature when the flaps are inserted during the packaging process to seal the box. First time opening of the box leads to visible, irreversible damage. Alternatively, the opening flaps can incorporate a perforation that tears when the box is first opened.

A disadvantage of this solution is that boxes must be handled with great care in the packaging and shipping process to prevent premature opening. However, as tamper verification features are integrated directly into the structure of the folding box, additional materials such as glue or labels can be eliminated entirely. In addition, using special folding techniques can help manufacturers achieve optimal Overall Equipment Effectiveness (OEE) for their packaging line as they allow the speed of machinery to be maintained.

Advantages

- Additional materials such as glue or labels are unnecessary.
- Can help manufacturers achieve optimal OEE.

Disadvantages

- Boxes must be carefully handled to prevent premature opening.

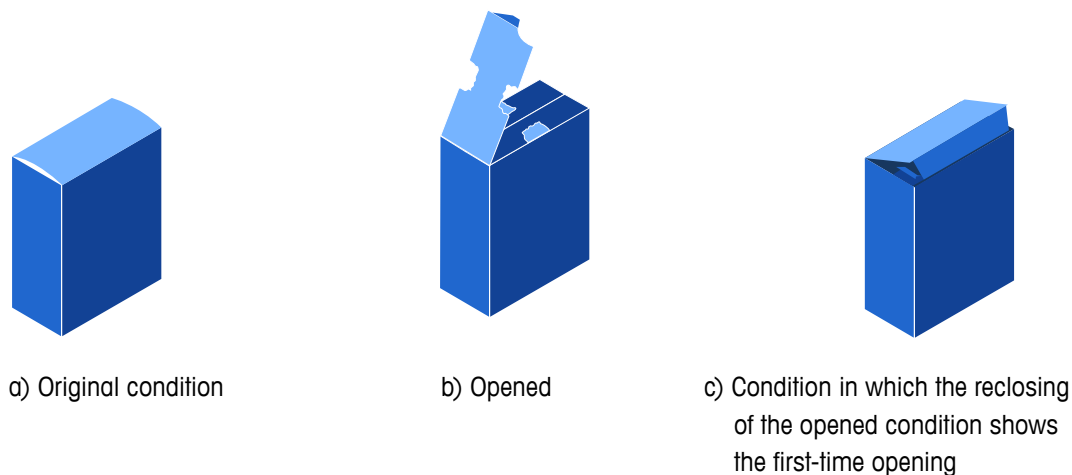


Figure 3: Example of a specially constructed folding box

4 Film Wraps

Another option to prevent unauthorized opening of medicinal products is to cellophane a filled folding box or shrink wrap it in a film, which must be ripped or broken to gain access to the product. However, both cellophane and film wrapping without additional safety features can be replaced at any time and do not protect the actual product. Another disadvantage of film wrapping is that it can reduce the readability of the serialization code on packaging, which could complicate a potential aggregation process where all serialization codes have to be read to generate an aggregation code. In addition, cellophane makes it more difficult to feel Braille dots.

Shrink wrapping can also prove tricky for elderly or disabled patients to remove. In addition, the cellophane must be joined to the folding box, for example by gluing, so that the supplying pharmacist can recognize whether the wrapping has been removed from the packaging.

Disadvantages

- Don't protect the actual product.
- Reduce the readability of serialization codes.
- Make it difficult to feel Braille dots.
- Can be tricky to remove.
- Must be joined to the box.



Figure 4: Example of a film wrapper

5 Adhesive Seals

Self-adhesive seals that have to be destroyed before a box is opened for the first time provide another tamper-evident solution. A number of options are available, including adhesive tear-off labels that damage the surface of a box when pulled off, or void seals that leave behind a visible pattern or text when removed. Additional options include tamper-proof labels with perforations and those made of ultra-destructive specialty film.

Among the various security options, the advantage of sealing with labels is that the packaging itself does not need to be altered, which means that existing packaging machines do not require modification. Moreover, such labels are not merely restricted to folding boxes; they can also be used to seal fluid containers such as bottles or ampoules.

Applying a label to the sealing edge of a folding box provides secure tamper evidence. In addition to protecting against manipulation, this method provides the option to integrate security features into the product label.

Advantages

- Packaging doesn't need to be altered.
- Packaging machines don't require modification.
- Can be used to seal boxes and fluid containers.
- Security features can be integrated into product labels.

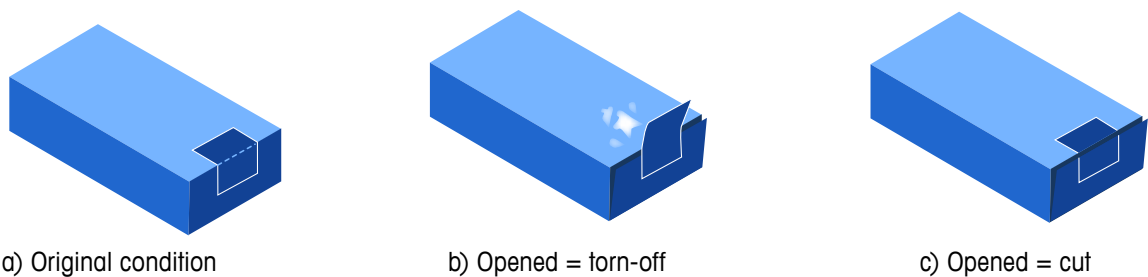


Figure 5: Example of a sealing label or tape

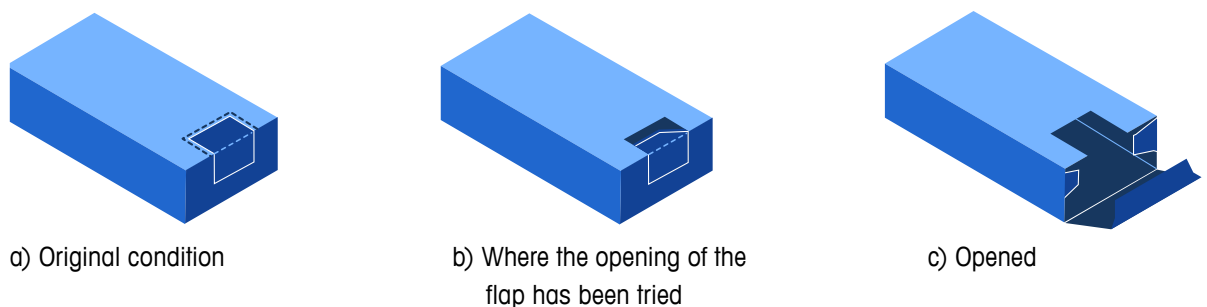


Figure 6: Example of a folding box with perforations closed with a label or tape

6 Complete Marking, Verification and Tamper-evident Sealing Solutions

Complete solutions are available which are designed to help pharmaceutical companies comply with all the specifications of EU Directive 2011/62/EU and DIN EN 16679 governing protection against falsification. Such systems combine components for serialization, tamper-evident sealing and process monitoring, and can be easily integrated into both new and existing packaging processes, and networked with data management systems.

An inkjet labeling system prints each item of pharmaceutical packaging with a unique serial number and data matrix code for end-to-end traceability. A smart camera then verifies the barcode and number. The sealing module, which is compliant with EN 16679, then seals the tabs of cardboard boxes with a transparent tamper-evident seal. This ensures that any attempt to open the packaging leaves behind visible traces, providing evidence of tampering. Finally, an integrated reject system collects all the packaging that has been identified as faulty, for example where the serial number printing has been deemed illegible, in a storage container.

The decision to opt for a complete solution supplier offers the following advantages:

- One point of contact for all systems concerned.
- A single supplier of ordered components, rather than several equipment suppliers.
- Compatibility of components with a single software system for management of the entire process.
- Combined systems are more compact, allowing easier line integration, and have fewer moving parts, thereby reducing maintenance time and cost.
- Reduction of user interfaces minimizes operation errors and makes product changeovers faster and more efficient, reducing downtime.
- Increased Overall Equipment Effectiveness (OEE)

7 Conclusion

A tamper-evident solution is essential to comply with EU Directive 2011/62/EU. By allowing pharmaceutical manufacturers and packaging companies to decide how they meet the regulations, the EU allows leeway for implementation approaches that are optimally adapted to individual's financial and technical circumstances.

This white paper has provided an overview of the four main tamper evident solutions outlined in EN 16679: gluing, special folding techniques, film wraps and adhesive seals. Whichever solution pharmaceutical manufacturers and packaging companies choose, it is important they ensure all products produced are in compliance. Doing so will help to ensure patient safety and the marketability of their products, as well as help to restore trust in the pharmaceutical industry by guaranteeing the authenticity of medicines.

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