ISO/TC 122 N

Date: 2017-08-01

ISO/WD 21976:2017(E)

ISO/TC 122/SC /WG 15

Secretariat: JISC

Packaging — Tamper verification features for medicinal product packaging

Emballage — Témoins d'effraction pour emballages de produits médicinaux

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Document type: International Standard
Document subtype:
Document stage: (20) Preparatory
Document language: E

X:\TA1\TG1-1\NAVp\Gremien\NA115\NA115_01_FB\NA115_01_03_02_AK\Projekt\ISO NP 21976\2017-06-29 für Enquiry\Manuscript_for_ISO_DIS_21976_(E).docx STD Version 2.8l

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Foreword

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The committee responsible for this document is ISO/TC 122 *Packaging*.

Introduction

Requirements for tamper verification features on medicinal product packaging are emerging and expanding globally to further improve patient safety.

This International standard is to support the harmonization and implementation of tamper verification features to the packaging of medicinal products worldwide.

The knowledge and experience that has been gained in EN 16679:2014 was the base for developing this International Standard.[1)]

1) The background for the creation of a European Standard for tamper verification features for medicinal product packaging (EN 16679) was the European Directive 2001/83/EC [1], as amended by Directive 2011/62/EU [2], the latter commonly referred to as the "Falsified Medicines Directive" (FMD).

Packaging — Tamper verification features for medicinal product packaging

1 Scope

This International Standard specifies requirements and provides guidance for the application, use and check of tamper verification features to the packaging of medicinal products.

Note: The packaging of medicinal products placed on the market and incorporating tamper verification features in accordance with this International Standard meets, as an example but not limited to, the requirements of Directive 2001/83/EC [1] as amended by Directive 2011/62/EU [2]. Article 54(o) of the Directive stipulates, that on the outer packaging of certain 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 principles in this International Standard can be applied in other countries, jurisdictions and sectors, as appropriate.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

There are no normative references in this document.

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
falsified medicinal product
medicinal products that deliberately/fraudulently misrepresent their identity, composition or source

[SOURCE: WHO, Definitions of Substandard and Falsified (SF) Medical Products, 2017]

3.2
finished product
authorized medicinal product which has undergone all stages of production including packaging in its final container as it is dispensed, sold or otherwise supplied

3.3
immediate packaging
primary packaging
container or other form of packaging directly in contact with the medicinal product

[SOURCE: ISO 21067:2016, 2.2.3 – modified]

3.4
manufacturing authorization holder
natural or legal person or entity that is authorized for total or partial manufacture

Note 1 to entry: This includes replacement of safety and tamper verification features (in accordance with Directive 2001/83/EC [1], Article 47a(1)(b) as amended by Directive 2011/62/EU [2]).

3.5
marketing authorization holder
natural or legal person or entity responsible for placing the medicinal product on the market

3.6
medicinal product
any substance or combination of substances that may be administered to human beings (or animals) for treating or preventing disease, with the view to making a medical diagnosis or to restore, correct or modify physiological functions

[SOURCE: ISO 11615:2012, 3.1.49]

3.7
outer packaging
secondary packaging
packaging designed to contain one or more primary packagings together with any protective materials where required

[SOURCE: ISO 21067:2016, 2.2.4 – modified]

3.8
tampering
unauthorized attempt to open, manipulate or re-use the packaging or elements of it

3.9
tamper verification feature
characteristic(s) allowing verification of whether the outer packaging of medicinal products or, where there is no outer packaging, the immediate packaging has been opened or tampered with

Note 1 to entry: Tamper verification “features” may be referred to as “anti-tampering devices”

3.10
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

[SOURCE: ISO 9000:2015, 3.8.12]

4 General requirements

4.1 Tamper verification features

Tamper verification features shall be applied to packaging of medicinal products as required by legislation or may be applied for other situations.

4.2 Purpose of tamper verification features

Tamper verification features should provide an indication that the outer packaging of a finished product has been opened or tampered with, i.e. indicating a possible adulteration or unauthorized attempt to open the packaging or entry of falsified medicinal products into the legitimate supply chain. Tamper verification features limit the ability to replace the contents of genuine packs.

Tamper verification features are only one element of possible safety features against falsification and will not by themselves prevent falsification of medicinal products.

4.3 Application and use of tamper verification features

The application of tamper verification features shall not compromise the readability of statutory information. The statutory text on the packaging should remain readable after opening the pack.

Applying tamper verification features may increase the physical strength needed to open the packaging.

4.4 Check of tamper verification features

The tamper verification feature should enable a visual check for its presence and any evidence of tampering (see 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9 and 5.10 for details).

The immediate packaging of medicinal products may also provide tamper verification. This serves a different purpose, most significantly to prevent interference with the medicinal product itself and does not meet the tamper verification requirements in certain jurisdictions. However it also provides another level of protection against tampering.

5 Categories of tamper verification features

5.1 General

Tamper verification technologies applied on the packaging are under constant evolution. Nine broad categories of tamper verification features are described in this International Standard (see 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9 and 5.10). Other tamper verification features may exist or be developed and shall meet the requirements of this International Standard as appropriate. The illustrations in Clause 4 are non-exhaustive.

Annex A provides additional information on tamper verification features as listed in 5.2 to 5.10.

If there is no outer packaging, the immediate packaging (e.g. bottles and tubes) shall be equipped with a tamper verification feature in accordance with 5.4 to 5.10.

Tamper verification features shall meet the requirements of Clause 4.

The marketing authorization holder shall decide on appropriate tamper verification feature(s) out of the following (see 5.2 to 5.11).

This choice may be based on an assessment that takes into account a number of factors including technical feasibility, appropriateness, effectiveness, other safety features used on the product, and overall cost.

5.2 Folding boxes closed with glue

5.2.1 Description

A glue, e.g. hot melt, polyurethane, dispersion or other glues, or a combination of glues is applied to close the folding box. These boxes may incorporate perforations to facilitate the opening of the pack.

5.2.2 Criteria of tamper verification

Folding boxes closed with glue shall be cut or torn to gain access to the product. The box cannot be opened without visual tear-off/ripping-off of the carton board surface and/or other parts of the folding box.

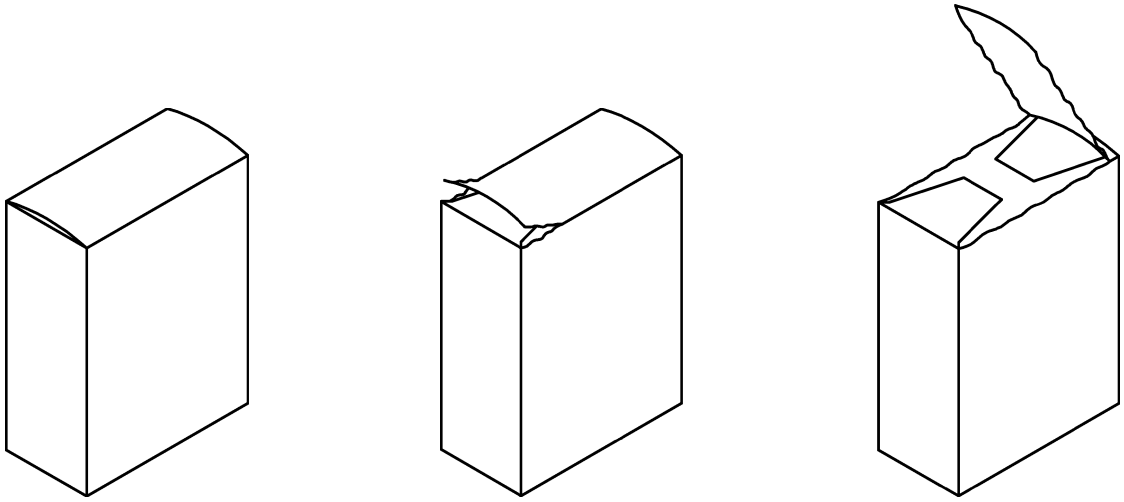
5.2.3 Verification

First time opening of the folding box leads to visible, irreversible damage of the folding box integrity, for example (see Figure 1 and Figure 2):

— damage of one or more of the flaps (see Figure 1 b) and Figure 1 c));

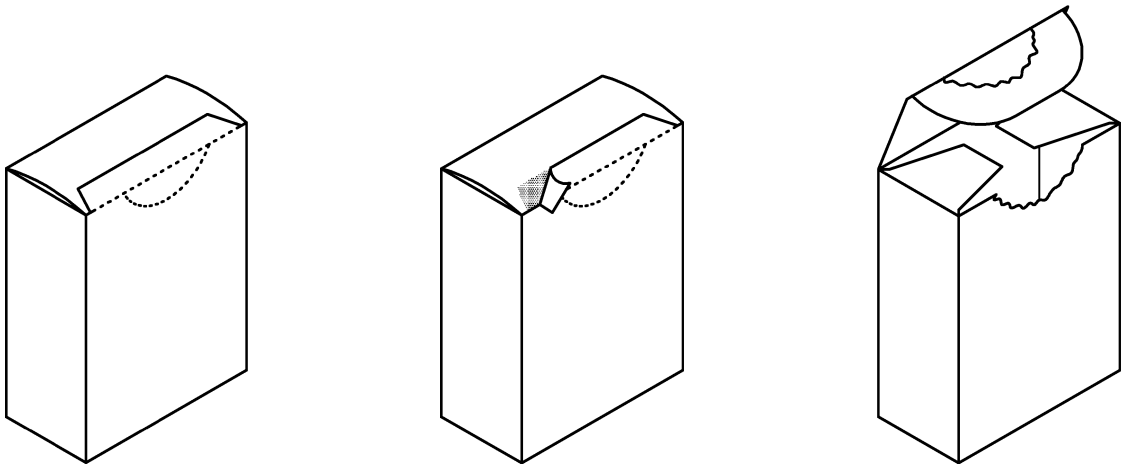
— damage of perforations (see Figure 2 b) and Figure 2 c));

— damage of other parts of the folding box.



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

5.3 Specially constructed folding boxes

5.3.1 Description

The flaps and the body of the folding box are constructed in such a way that the feature is activated/enabled by inserting the flaps by the manufacturer to close the folding box. First time opening leads to a visible, irreversible change of the folding box appearance in such way, that parts of the flaps or of the folding box are damaged.

5.3.2 Criteria of tamper verification

The closure is set up in such a way that, the first time the box is opened, parts of the flaps or of the folding box are ripped off and/or are torn.

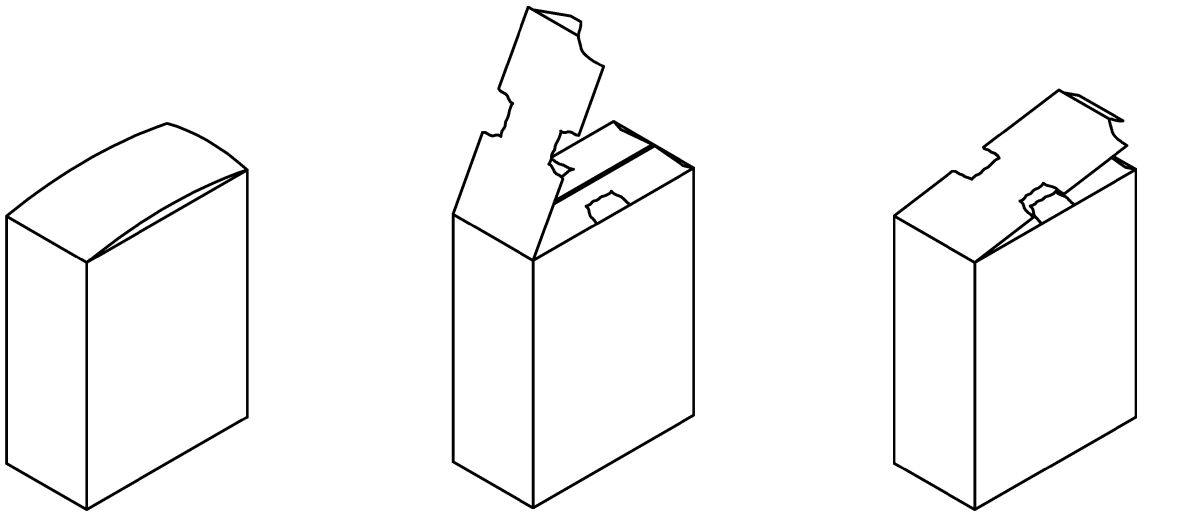
5.3.3 Verification

First time opening leads to visible, irreversible damage of the folding box integrity for example (see Figure 3):

— damage of one or more of the flaps (see Figure 3 b) and Figure 3 c));

— damage of perforations and/or scores/half cuts, if applicable;

— damage of other parts of the folding box.



a) Original condition **b) Opened** **c) Condition in which the reclosing of the opened condition shows the first time opening**

Figure 3 — Example of a specially constructed folding box

5.4 Sealing labels and tapes

5.4.1 Description

A label or tape (e.g. from paper, film or laminate) is applied in order to seal the packaging of medicinal products. The packaging to be sealed may incorporate perforations to facilitate the opening of the pack. The sealing label or tape shall provide the integrity of the sealed packaging.

5.4.2 Criteria of tamper verification

Tampering of the sealing label or tape or opening of the packaging shall lead to visible, irreversible damage or change of the packaging and/or of the label or tape.

5.4.3 Verification

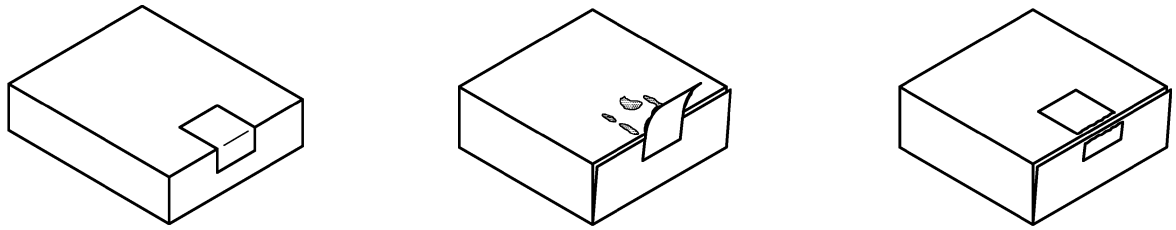
Verification of typical categories of sealing labels or tapes (see Figure 4 and Figure 5) are:

1) **Fibre-tear seal**: By tampering/tearing off the sealing label or tape the fibre or the surface of the packaging is torn or ripped off and thus clearly indicates a visible, irreversible damage or change of the packaging.

2) **Void seal**: By tampering/tearing off the sealing label or tape a hidden pattern or text of the sealing label or tape becomes irreversibly visible on the sealing label or tape and/or on the packaging.

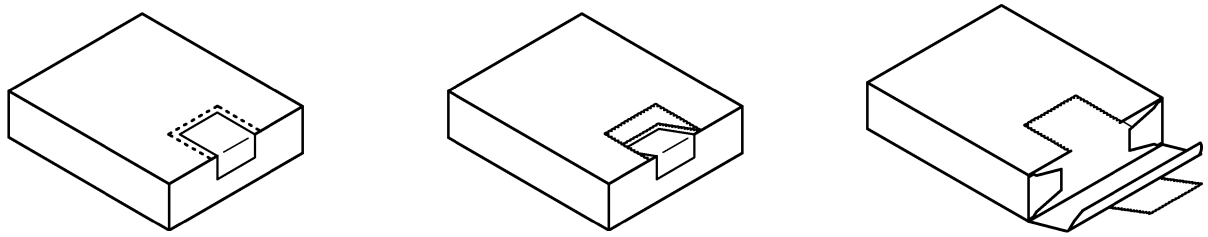
3) **Seal made with opening strips or perforations**: By tampering or opening or tearing off the sealing label or tape the sealing label or tape becomes irreversibly torn, broken or peeled off and indicates that the individual product container has previously been sealed.

4) **Seal made of fragile material**: By tampering or opening or tearing off the sealing label or tape the sealing label or tape becomes irreversibly torn or broken.



a) Original condition **b) Opened = torn-off** **c) Opened = cut**

Figure 4 — Example of a sealing label or tape



a) Original condition **b) Where the opening of the flap has been tried** **c) Opened**

Figure 5 — Example of a folding box with perforations closed with a label or tape

NOTE Further examples for sealing labels or tapes are bespoke tamper-evident void seals and seals with opening strip.

5.5 Film wrappers

5.5.1 Description

The product container or part of it is wrapped in film ensuring the product is appropriately sealed. The film shall be torn to gain access to the product.

5.5.2 Criteria of tamper verification

Tampering or opening shall lead to visible, irreversible damage or change of the film wrapper and show visible evidence of tampering.

5.5.3 Verification

First time opening leads to visible, irreversible damage of the film wrapper and provides the indication that the outer package has been tampered with. The film wrapper cannot be removed and resealed without showing visible evidence of tampering (see Figure 6).

It may be appropriate to indicate that a film wrapper should be present.

a) Original condition **b) Opened**

Figure 6 — Example of a film wrapper

5.6 Sleeves

5.6.1 Description

A film is shrunk around the immediate packaging or at least around its closure, where the film adapts to the outer shape. The sleeve shall be ripped or broken to gain access to the product.

5.6.2 Criteria of tamper verification

Tampering or opening shall lead to visible, irreversible damage or change of the sleeve and show visible evidence of tampering.

5.6.3 Verification

First time opening leads to visible, irreversible damage of the sleeve and provides the indication that the immediate packaging or its closure has been tampered with. The sleeve cannot be removed and resealed without showing visible evidence of tampering (see Figure 7).

It may be appropriate to indicate that a sleeve should be present.

a) Original condition **b) Opened**

Figure 7 — Example of a sleeve shrunk around a closure of a bottle

5.7 Breakable or tear-away closure

5.7.1 Description

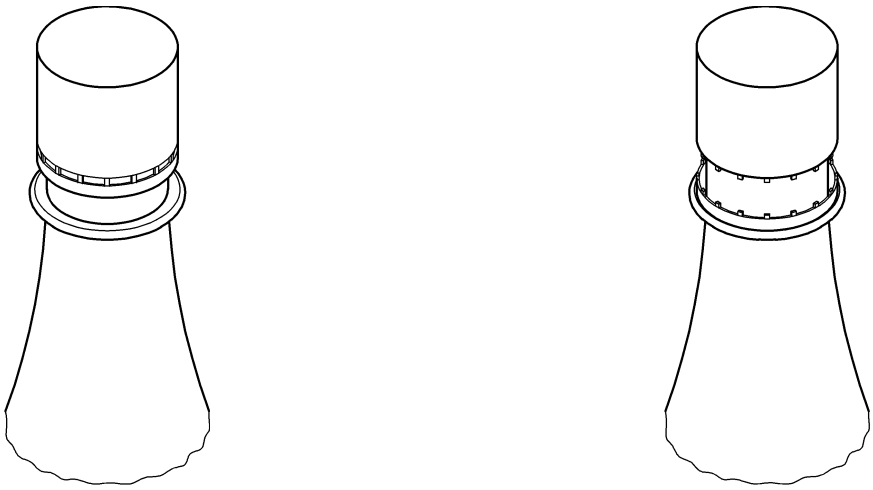
The product container is closed with a breakable or tear-away closure, made of metal or plastic that has a portion that breaks on opening.

5.7.2 Criteria of tamper verification

Tampering or opening shall lead to visible, irreversible change in the closure and show visible evidence of tampering.

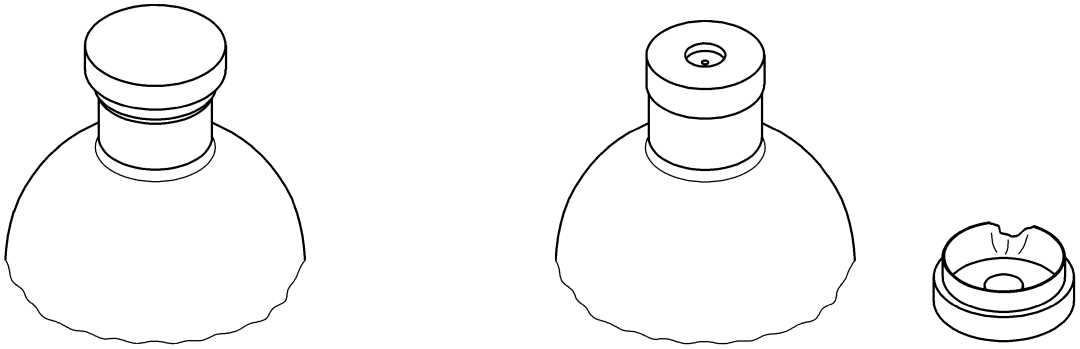
5.7.3 Verification

First time opening leads to visible, irreversible change in the closure. The closure cannot be removed and reapplied in its original state without showing visible evidence of tampering (see Figure 8 and Figure 9).



a) Original condition **b) Opened**

Figure 8 — Example of a breakable closure



a) Original condition **b) Opened**

Figure 9 — Example of a tear-away closure

5.8 Display blister pack

5.8.1 Description

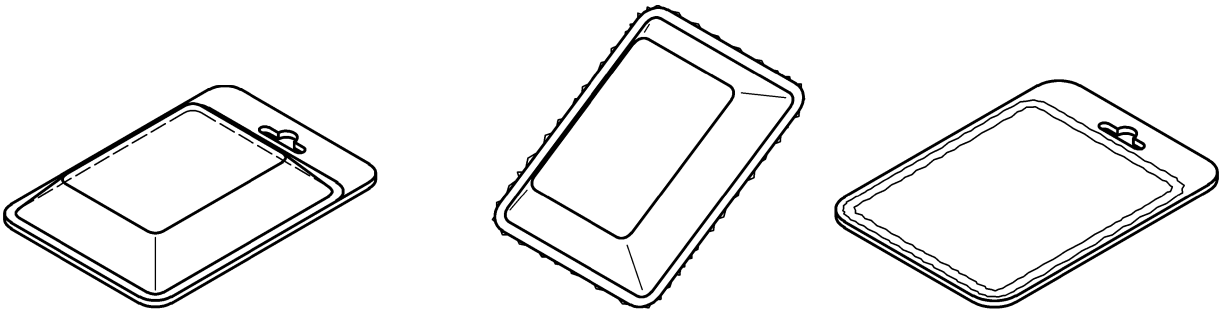
The product is sealed into a display blister pack which shall be cut or broken to gain access to the product. The display blister pack shall be intact and sealed all the way around.

5.8.2 Criteria of tamper verification

Tampering or opening shall lead to visible, irreversible damage or change of the display blister pack and show visible evidence of tampering.

5.8.3 Verification

First time opening leads to visible, irreversible damage of the display blister pack and/or its sealing. The display blister pack cannot be opened and reclosed without showing visible evidence of tampering (see Figure 10).



a) Original condition **b) Opened**

Figure 10 — Example of a display blister pack

5.9 Flexible packaging

5.9.1 Description

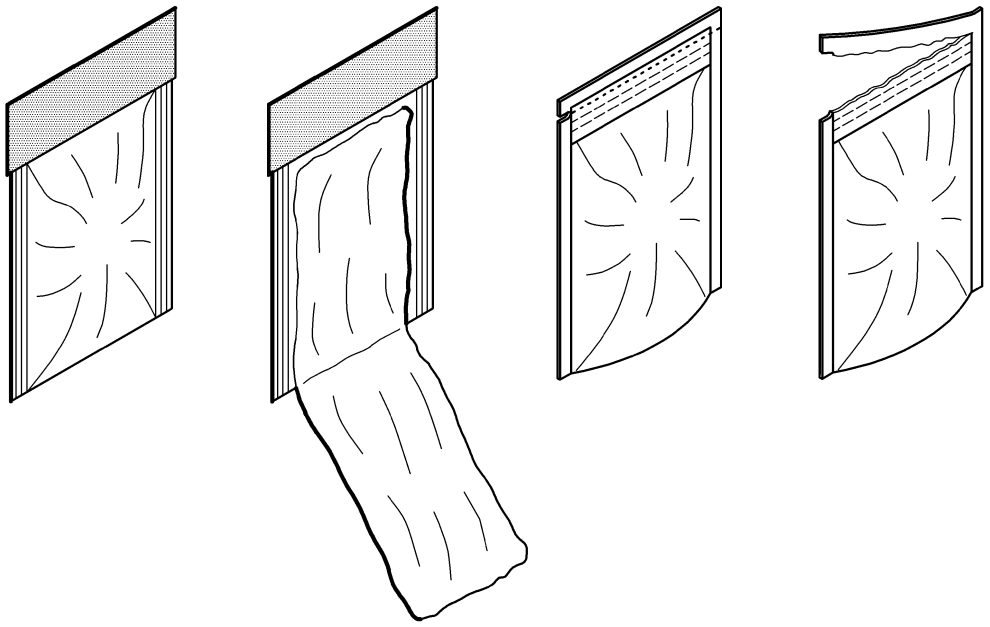
The medicinal product is sealed into a film or foil or combination thereof, e.g. pouches, sachets. The packaging shall be cut or torn to gain access to the product.

5.9.2 Criteria of tamper verification

Tampering or opening shall lead to visible, irreversible damage or change of the flexible packaging and show visible evidence of tampering.

5.9.3 Verification

First time opening leads to visible, irreversible damage of the flexible packaging and/or its sealing. The flexible packaging cannot be opened and reclosed without showing visible evidence of tampering (see Figure 11).



a) Original condition **b) Opened** **c) Original condition** **d) Opened**

Figure 11 — Two examples of a flexible packaging

5.10 Blow-fill-and-seal-container (BFS)

5.10.1 Description

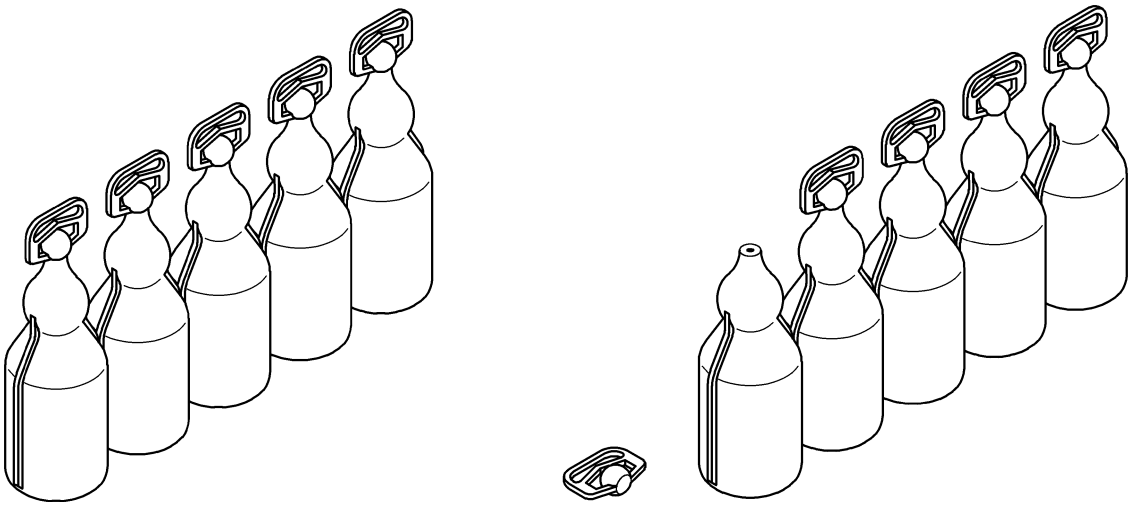
The BFS container is made from plastic material and is formed, filled and sealed in a continuous process. The BFS container shall be penetrated or broken to gain access to the product.

5.10.2 Criteria of tamper verification

Tampering or opening shall lead to visible, irreversible damage or change of the BFS container and show visible evidence of tampering.

5.10.3 Verification

First time opening leads to visible, irreversible damage of the BFS container. The BFS container cannot be opened and reclosed without showing visible evidence of tampering. Squeezing may be recommended in order to check that the BFS container does not leak (see Figure 12).



a) Original condition **b) Opened**

Figure 12 — Example of a blow-fill-and-seal-container

5.11 New and emerging technologies

Other tamper verification features may be developed and shall meet the requirements of this International Standard as appropriate.

Annex A
(informative)

Additional information regarding tamper verification features

Table A.1

Category	Description
General comments	• Tamper verification features are used in sectors other than for medicinal products. • There may be a regulatory impact and a notification required if there are layout or artwork changes. • Change management costs may occur.
Folding boxes closed with glue	• Immediately visible if folding box is glued or not if appropriate design is used. • Perforations may facilitate opening as intended.
Specially constructed folding boxes	• Tamper verification features are included in the design of the folding box.
Sealing labels and tapes	• There is a variety of label materials, constructions and visual effects to indicate the opening of the package. • Perforations or opening flaps may facilitate opening as intended.
Film wrappers	• The use of tear tape or perforations may facilitate opening as intended.
Sleeves	• The use of tear tape or perforations may facilitate opening as intended.
Display blister packs	• Perforations may facilitate opening as intended.
Tamper verification features on immediate packaging	• Tamper verification features, such as described in 5.4, 5.5, 5.6 and 5.7, may be included in the closure of the immediate packaging. • Perforations or other opening aids may facilitate the opening of the closure (e.g. caps) as intended.

Bibliography

Further information can be obtained from the website sources given below. This list is non-exhaustive and the information available given should not necessarily be treated as authoritative. Any proposed action taken using such information should be checked against local regulatory requirements.

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