Technical Paper on Tamper-Evidence and First Opening Indication

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1 Introduction

The pharmaceutical industry is countering the proliferation of counterfeit and illicit medicines with a variety of security technologies that make it significantly more difficult to virtually impossible for a criminal to succeed in tampering with genuine products. Depending on the threat scenario (diversion, falsification, theft, re-use of genuine packaging, etc.) different tools are available to tackle the challenge.

The re-use of original packaging, however, poses a rather new and challenging threat scenario and calls for new and different functionalities on the part of the packaging components.

The specific challenge in the case of packaging re-use is that authentication (security) and / or product identity (serial number) features may be integrated into the packaging components and could be re-used as well. Furthermore, the presence and validity of these features on genuine packaging components can give the false impression that the content of a refilled container matches the label. Thus, new mechanisms that allow for clear, irreversible and tamper-evident indication of initial opening / first use, as well as destruction of product identifiers and authentication features should also to be taken into account.

Pharmaceutical packaging should to be designed in a way that provides the end-user (e.g. healthcare professional, patient) with clear and easily identifiable information as well as visual or haptic indication that the product which is about to be administered may not be genuine. If parts of the packaging are irreversibly destroyed upon opening, the criminal has to invest time, money and know-how to reverse-engineer the packaging into a state which mimics the intact original. This implies that a previous opening indication would have to be combined with partial, or complete destruction or devaluation of authentication and product identity features.

Purpose
Clearly indicate that the packaging of a finished product has been opened or tampered with
Prevent re-use of genuine packs and relevant security features on it
Limit the ability to replace the contents of genuine packs
Proof of sterility up to point of use
Prevent multi-use of a single dose medication
Alert consumers of possible safety concerns before they purchase or use goods[1]

Table 1 Purpose of tamper-evidence and first-opening indication systems

[1] https://www.tga.gov.au/sites/default/files/code-practice-tamper-evident-packaging-therapeutic-goods.pdf

2 Definitions

The table below summarizes the official definitions from various regulatory and standards organizations of key terms used in connection with tamper-evident solutions and should allow consistent use of those terms.

Source	Term	Definition
ISO 21976 International Standard Packaging — "Tamper verification features for medicinal product packaging"	Tampering	Unauthorized attempt to open, manipulate or re-use the packaging or elements of it
	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.
Title 21 – Food and Drugs Chapter I –Subchapter C – Drugs: General Part 211 – current Good Manufacturing Practice for finished Pharmaceuticals, Subpart G--Packaging and Labeling Control, Sec. 211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products. (USA)	Tamper-evident packaging	A tamper-evident package 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. To reduce the likelihood of successful tampering and to increase the likelihood that consumers will discover if a product has been tampered with, the package is required to be distinctive by design or by the use of one or more indicators or barriers to entry that employ an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture). https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=211.132
Code of practice for tamper-evident packaging of therapeutic goods V2.0 May 2017 (Australia)	Tamper evident packaging (TEP)	Tamper evident packaging (TEP) means packaging that has 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 may have occurred. https://www.tga.gov.au/sites/default/files/code-practice-tamper-evident-packaging-therapeutic-goods.pdf
Code of practice for tamper-evident packaging of therapeutic goods V2.0 May 2017 (Australia)	Tamper-evident features	Tamper-evident features are barriers or devices on the packaging, which if breached or missing, reveal irreversibly to consumers that tampering may have occurred. https://www.tga.gov.au/sites/default/files/code-practice-tamper-evident-packaging-therapeutic-goods.pdf
Guideline for the Tamper-Evident Packaging of Medicines, Complementary Healthcare	Tamper proof	"Tamperproof" (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. https://www.tga.gov.au/sites/default/files/packaging-tamper-evident-guideline-001222.pdf

Table 2 Selected definitions used in other guidelines or regulations.

3 Overview of selected Regulations and Guidelines

Country	Year	Regulation/Guideline	Link
Argentina	2012	Regulation 1831/ 2012	http://www.anmat.gov.ar/webanmat/Legislacion/Medicamentos/Disposicion_1831-2012.pdf
Australia	2017	Guideline "Code of practice for tamper-evident packaging of therapeutic goods V2.0 May 2017"	https://www.tga.gov.au/sites/default/files/code-practice-tamper-evident-packaging-therapeutic-goods.pdf
Brasil	2009	Resolution No. 71, Dec 22, 2009 Establishing rules for drug labeling.	http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2009/res0071_22_12_2009.html
EU	2019	EU 2016/161, DIN 16679 "Anti-Tampering Device"	https://ec.europa.eu/health/human-use/falsified_medicines_de
Malaysia	1984	Hologram Security Device (Meditag TM) Regulation 8(1) of the Control of Drugs and Cosmetics Regulations 1984	https://www.npra.gov.my/index.php/en/component/content/article/37-english/faq/623-product-registration.html?Itemid=1391
Saudi Arabia	2019	Guideline for the Tamper-Evident Packaging	https://www.sfda.gov.sa/en/drug/drug_reg/Pages/default.aspx?catid=17&news=Main
Switzerland	2019	In order to guarantee an equivalent level of protection against counterfeit medicines in Switzerland, Art. 17a of the Swiss Medicines Act (HMG) stipulates that this should be integrated into the Swiss Therapeutic Products Act. The entry into force of this article is planned together with a corresponding ordinance. Both are expected to enter into force at the end of 2019 after the ordinance has been consulted. Contrary to EU law, the attaching of safety features and their examination in accordance with Art. 17a HMG is still voluntary.	https://www.smvo.ch/en/
USA	1982	Title 21 – Food and Drugs Chapter I –Subchapter C – Drugs: General Part 211 – current Good Manufacturing Practice for finished Pharmaceuticals, Subpart G--Packaging and Labeling Control, Sec. 211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products. (USA)	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.132

Table 3 Overview of global regulation and guidelines

4 Technology Overview

4.1 Primary Packaging and Add-On Tamper-Evidence Solutions

This section provides an overview of the current state of the art of primary packaging tamper evident solutions. The selection is focused on the ability of the solution to irreversibly indicate the initial opening of the container. Due to the great diversity of different containers and container materials, this listing is limited to the most used container classes and materials. The following table offers an overview of primary container closures, the covered sizes and their principal ability to indicate first-opening or tampering.

Primary Packaging	Material	Tamper-Indication	Available Closure/Cap Systems	Covered Sizes
Vials	Glass/ COC/COP	x	Flip-Off Caps (Aluminium) Plastic flip-off caps are easily removable to expose the underlying aluminum seal and the injection target area. During the opening process a plastic piece is breaking out.	full range
	Glass	x	All plastic closure (no Aluminium) with integrated stopper for one-step assembly without crimping. The plastic flip-off caps are easily removable to expose the underlying injection target area. During the opening process plastic pieces are breaking out.	13 mm Vials 20 mm Vials
Prefilled Syringe *Luer Lock*	Glass		Standard flexible or rigid tip caps Opening through normal screwing, with no Tamper-Evidence	full range
		x	Luer lock closure with integrated tamper-evident flags which pop up upon opening	1-3 ml
		x	Luer lock closure, which is tilted back and forth until the cap disconnects, the plastic seals break and the cap can be pulled off.	1-3 ml
Prefilled Syringe *Luer Lock*	COC/COP		Standard flexible or rigid tip caps Opening through normal screwing, with no Tamper-Evidence	full range
Prefilled Syringe *Staked-In*	Glass		Standard flexible needle shields/rigid needle shields with no tamper-evidence	full range
		x	A rigid needle-shield with a tamper-evidence that has a portion (such as a ring) that breaks away on opening and remains on the neck of the container.	1 ml long, 1.5 ml
		x	The syringe is opened by separating the syringe cap from the ring in a steady, axial movement.	1 ml long
		x	Special syringes that are designed in a way to ensure the needle does not stick into the tamper-evident needle shield, preserving the needle's sharpness. The pinch seals automatically disengaged upon pulling the rigid needle shield to break the tamper-evident ring.	0.5-3 ml

Prefilled Syringe *Staked-In*	COC/COP		Standard flexible needle shields/rigid needle shields with no tamper-evidence	1 ml 2.25 ml
Blister or Strip Packs		x	Individual doses (for example, capsules or tablets) are sealed in pockets, separated and individually protected. The individual compartment of the pack must be ripped or broken to gain access to the product. The layers forming the blister or strip pack cannot be separated or replaced without leaving visible evidence of entry.	
Solid Dose Containers	(e.g.) HDPE, Glass	x	Induction seals/ inner mouth seals	full range
		x	Closure has a portion (such as a ring) that breaks away on opening and remains on the neck of the container.	full range
Tubes	Laminate, Aluminium barrier	x	Closed orifice under the cap that is being punctured to gain access to the tube	wide range available
		x	Peel Seal under the cap that is being removed to gain access to the tube	
		x	Cap with tear-off band	
		x	Flip-top cap with tear-off band	
		x	Tube with non-perforated top to cut off	

Please note: This overview does not claim to be complete.

Table 4 Overview of primary container closures, available fill ranges and their principal ability to indicate first-opening or tampering

As table 4 suggests there are primary container packaging options that don't provide an integrated tamper-evidence feature. Some of the aforementioned features might also not be efficient enough, depending on the specific threat and product (see chapter 5) and thus it might be necessary to add additional tamper-evidence functionality for enhanced security or for a different stakeholder in the supply chain to verify.

Tamper evidence solutions can be categorized by the level of protection they provide against possible manipulation, re-use or re-purchasing of products or packaging components.

Level 0: The solutions provides **no indication** of prior opening or are easily defeated or replaced.

Level 1: The solution provides some evidence of prior opening although it is possible to over-come this evidence with **minimal effort**. Tamper-evident components with no or unspecific, unbranded designs are easier to be re-used or replaced.

Level 2: The solution provides clear evidence of prior opening although it is possible to over-come this evidence with **medium effort** though manipulation, re-use or reverse-engineering of components or the use of generic components. Tamper-evident components with specific, branded designs pose a higher hurdle to be replaced.

Level 3: Re-use of genuine packaging or opening of genuine packaging in a manipulative way is not possible or practical. Normal opening results in significant destruction of the packaging closure or components, so that they cannot be re-used. Re-purchasing or reverse engineering requires **significant effort** or high technical infrastructure or capability.

The TE levels given in the tables below are in some cases given in ranges. This represents the large variety of different add-on tamper-evident solutions that differ in complexity with respect to construction and design, resulting in different levels of tamper-evident protection.
Please note that the below mentioned list of both initial packaging closures and additional tam-per-evident solutions may not be complete and represents the status of available solutions at publication date.

Table 5 summarizes solutions that could be added to the primary packaging listed in table 4 to add or enhance the tamper-evidence of the said packaging.

Primary Packaging	Material	TE	Initial Closure/Cap Systems	TE	Additional Tamper Evident Options	
Vials	Glass	L1	Flip-Off Caps (Aluminum)	Additional TE options for both glass/COC/COP	L1-L2	Shrink label: Performs both sealing and labeling function. It is shrunk by heat to tightly seal the union of the cap and container. The label must be ripped or broken to gain access to the product. A perforation can be added for easy opening.
	COC/COP (Cyclic Olefin Copolymer/ Polymer)	L1	Plastic flip-off caps are easily removable to expose the underlying aluminum seal and the injection target area. During the opening process a plastic piece breaks off.		L3	Cap-Label Concept: A combination of one or two (bottom and top) plastic caps, that are attached with a label and serve as a second layer. Different opening mechanisms via perforation or opening stripe are possible. Tamper-evidence is achieved through defacing of the label and/or destruction of the cap.
	Glass	L1	All plastic closure with integrated stopper for one-step assembly without crimping. The plastic flip-off caps are easily removable to expose the underlying injection target area. During the opening process plastic pieces break off.		L2	A label that covers both container body and closure cap: Upon opening, the label's tear strip is removed and previously invisible inscriptions appear on the label. Tamper-evidence is achieved through both destruction of the label and appearance of designs.

Primary Packaging	Material	TE	Initial Closure/Cap Systems	TE		Additional Tamper Evident Options
Prefilled Syringe **Luer Lock**	Glass	L0	Standard flexible or rigid tip caps Opening through normal screwing, with no Tamper-Evidence	Additional TE options for both glass and COC/COP	L2-L3	A label that extends beyond the cap and forms a label-based closure. Upon opening via perforation or opening stripes the label is destroyed and the label-based closure can be removed together with the needle shield.
		L1	Luer lock closure with integrated tamper-evident flags which pop up upon opening			
		L2	Luer lock closure, which is tilted back and forth until the cap disconnects, the plastic seals break and the cap can be pulled off.			
	COC/ COP	L0	Standard flexible or rigid tip caps Opening through normal screwing, with no Tamper-Evidence		L1-L2	Seal labels around the transition of the cap/body: Upon opening the seal is destroyed and shows a clear color indication.
					L1-L2	Seal labels connecting one or both sides of the container via the top of the cap: Upon opening the seal is destroyed on one or both sides.
					L1-L2	Shrink labels: The shrink label performs both sealing and labeling function and is shrunk by heat to tightly seal the union of the cap and container. The seal must be ripped or broken to gain access.
					L2-L3	Cap-Label Concept: An adapter cap is applied to the Luer Lock cap which makes the diameter of the cap the same as the diameter of the syringe in order to achieve readiness for standard labeling processes. The label performs both sealing and labeling functionality by covering both the cap and the syringe body. Tamper-evidence is achieved through destruction of the label and void effects or other visible indications.
Prefilled Syringe **Staked-In**	Glass	L0	Standard flexible needle shields/rigid needle shields with no tamper-evidence		L2-L3	A label that extends beyond the cap: The label is closed and thus forms a label-based closure. Tamper evidence is achieved by opening via perforation or opening stripes. After opening, the label is destroyed, and the label-based closure can be removed together with the needle shield.
		L1	A rigid needle-shield with a tamper-evidence that has a portion (such as a ring) that breaks away on opening and remains on the neck of the container.			
		L1	The syringe is opened by separating the syringe cap from the ring in a steady, axial movement.			
		L2	Special syringes that are designed in a way to ensure the needle does not stick into the tamper-evident needle shield, preserving the needle's sharpness. The pinch seals automatically disengaged upon pulling the rigid needle shield to break the tamper-evident ring.			
	COC/ COP	L0	Standard flexible needle shields/rigid needle shields with no tamper-evidence			

Primary Packaging	Material	TE	Initial Closure/Cap Systems		TE	Additional Tamper Evident Options
Blister or Stick Packs		L2	Individual doses are sealed in pockets, separated and individually protected. The individual compartment of the pack must be ripped or broken to gain access to the product. The layers forming the blister or strip pack cannot be separated or replaced without leaving visible evidence of entry.			
Solid Dose Containers	(e.g.) HDPE, Glass	L1	Induction seals/ inner mouth seals	Add-on TE	L1	Shrink label: Performs both sealing and labeling function and is shrunk by heat to tightly seal the union of the cap and container. The seal must be ripped or broken to gain access to the product. Perforation for easy opening.
		L1	Closure has a portion (such as a ring) that breaks away on opening and remains on the neck of the container.		L1-L2	Label Seal: The seal creates a tight union of the cap and container. The seal must be ripped or broken to gain access to the product. Perforation or opening stripe may be utilized for easy opening.
Tubes	Laminate, Aluminum barrier	L1	Closed orifice under the cap that is being punctured to gain access to the tube	Add-on TE	L1-L2	Shrink Sleeve: Performs sealing function and is shrunk by heat to create a tight union of the cap and container. The seal must be ripped or broken to gain access to the product. Perforations can be added for easy opening.
		L1	Peel Seal under the cap that is being removed to gain access to the tube			
		L1	Cap with tear-off band		L1-L2	Label Seal: The seal creates a tight union of the cap and container. The seal must be ripped or broken to gain access to the product. Perforation or opening stripe may be utilized for easy opening.
		L2	Flip-top cap with tear-off band			
		L2	Tube with non-perforated top to cut off			

Table 5 Overview of primary container closures, additional tamper-evident options and their respective TE Level.

4.2 Secondary Packaging

This section presents an overview of selected secondary packaging components, focusing on the ability to indicate the initial opening / tampering of the container in an irreversible way. Due to the great diversity of different container types and materials this selection is based on the most used container classes and materials.

Secondary Packaging	TE	Available Closure/Cap Systems[1]
Folding Carton	L0	**Locking Tabs:** The flaps and the body of the folding box are constructed in such a way that the feature is enabled by the manufacturer inserting the flaps to close the folding carton. First time opening leads to a visible, irreversible change of the folding carton appearance in such a way that parts of the flaps or of the folding carton itself are damaged.
	L0-L1	**Glue:** Folding carton sealed with adhesive must be cut or torn to gain access to the product. The box cannot easily be opened without visible signs of tear-off/ripping-off of the carton surface and/or other parts of the folding carton
	L2-L3	**TE Seal:** A paper, film or laminate label is applied in order to seal the packaging of medicinal products. Tampering of the sealing label or tape or opening of the packaging leads to visible, irreversible damage or change of the packaging and/or of the label or tape.
	L1	**Film Overwrap:** The film must be torn to gain access to the product. Tampering or opening shall lead to visible, irreversible damage or change of the film wrapper and creates visible evidence of tampering.
Blister Pack	L2	A blister pack must be cut or broken to gain access to the product. Tampering or opening results in visible, irreversible damage or change of the display blister pack and shows visible evidence of tampering.
Clamshell Packs	L1	The thermoformed containers provide a hinged lid and closures, which can be made re-closable or permanently sealed for tamper-evidence.
Flexible Packaging	L1	The medicinal product is sealed into a film or foil or combination thereof (e.g. pouches, sachets). The packaging is peeled, cut or torn to gain access to the product. Tampering or opening leads to visible, irreversible damage or change of the flexible packaging and show visible evidence of tampering.
Autoinjectors Injection Pens	L0	Autoinjectors and Injection Pens are usually not equipped with tamper-evident functionality.
	L1	The label performs both sealing and labeling functions covering both, cap and injector body. Tamper-evidence through destruction of the label and void or other visible indications.
	L2	Seal covering both cap and injector body. Tamper-evidence through destruction of the label and void or other visible indications.
The above-mentioned label-based solution´s tamper-evidence can be enhanced by the inclusion of visible designs (e.g. fine lines, wallpaper designs etc.) which are destroyed or defaced during opening as well as though the addition of authentication features. Also, digital technologies such as RFID/NFC technologies are beneficial in giving a digital response to the opening state. If they are integrated a Level L3 can be reached		
[1] ISO 21976 International Standard Packaging — "Tamper verification features for medicinal product packaging"		

5 Conclusion

This whitepaper provides the reader with an overview of terms, regulations, and guidelines with respect to tamper-evidence for pharmaceutical packaging components. Furthermore, a selection of closure systems of the most relevant primary and secondary packaging systems is presented and their ability to indicate first-opening or tampering is evaluated. Where available, solutions were listed that can complement and enhance the respective packaging level to compensate for the missing or insufficient functionality of a tamper-evidence/ first-opening indication.

The rising demand for such solutions is triggered by the increasing risk of product tampering and re-use of genuine packaging. This is generated by the complexity of the supply chain, the value of the drugs and the existence of a large underground economy for such goods. The potential risk to patient safety resulting from such illegal products is extremely high.

To secure a product´s integrity there are both packaging integrated solutions and add-on tamper-evident features available to consider. The breadth and scale of tamper-evidence protection features can be drawn from the previous tables. This tamper-evidence guidance can assist the industry to better differentiate those tamper-evident solutions that may be insufficient to pose a significant barrier from more effective solutions.

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