

PHARMACEUTICALS

EN-TAG™:

Ultra-miniaturized labels for authentication, security and drug safety



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1. The Global Challenges of the Pharmaceutical Industry

The globalization of the pharmaceutical industry has given rise to new challenges and the need for increased regulations and vigilance over the supply chain. The threat of counterfeited drugs in particular has been on the agenda of drug manufacturers, distributors and regulators for several years. A counterfeit medicine is a product whose origin, identity and/or ingredients have been falsely labeled; counterfeit medicines may include drugs that contain minimal or no levels of active ingredients.

The number of detected false medicinal products is on a steady rise. The World Health Organization estimates annual earnings from the global sales of counterfeit medicines in excess of \$32 billion. Moreover, in order to increase the volume of fake medicines, these products are channeled through the legal supply chain towards patients. The main sales channel for counterfeit medicines is the internet. The damage caused to patients and pharmaceutical companies by counterfeiters is therefore both costly and dangerous.

To combat the problem of counterfeit drugs, many of the world's leading pharmaceutical companies have directed efforts toward authenticating their packaging as part of the process of protecting their products. 2D data matrices and optically variable devices have become a widely used overt authentication feature on pharmaceutical products worldwide.



INTRODUCTION

Cold chain monitoring has also been a major challenge to the global pharmaceutical industry. Today more than ever, medicines must travel greater distances between production facilities and distribution centers and pharmacies. The distribution chain involves a number of storage and transit locations, including airports and docks. Drug distribution processes often involve lengthy clearance procedures at customs, several modes of transportation, numerous carriers and couriers, different climate zones and seasonal changes.

Exposure to temperature extremes can be disastrous for temperature-sensitive products. In less severe cases, shelf life can be shortened; in worst-case scenarios, products can be ruined. Biologics in particular are known to be most stable between 2-8°C. High-risk products include vaccines, insulins, blood products and other proteinaceous materials. These products must be protected from freezing; even a brief period at sub-zero temperatures may irreversibly denature the protein, leading to a loss of efficacy.

It is estimated that 4% of the cold-chain shipments en route to destination are subjected to a temperature excursion that may make the supplies unusable. Most inspectors and regulators indicate that the majority of temperature excursions happen because of problems in physical handling processes, lack of adequate procedures, training or simply awareness. A significant problem of transporting products between trailers and airplanes is the staging area, as carriers often need to stage freight outside of the aircraft for several hours before loading onto the aircraft, which can be a problem in extreme climates.

At the pallet level, drug makers have many options in order to ensure that their temperature-sensitive products move through the supply chain under appropriate



conditions, including time-temperature indicators, data loggers, RFID technology, passive or active insulated shippers and refrigerants.

However, none of these options can be exercised to monitor the thermal history of a drug *at the package level* (e.g. blister packs, bottles, caps, etc.).

2. A Changing Regulatory Environment

Increased demand by the competitive markets and legislators is forcing drug manufacturers to either change or modify their current drug manufacturing processes.

As regards to the rules for the medicines sold in the EU, the European Commission has proposed a number of legislative actions to ensure that certain categories of products bear a “safety-feature”, which would help to identify falsified products. Safety features may include individual product codes (“serialization”) on the packaging, which can be read by legal actors in the distribution chain, including pharmacies, or tamper-evident seals, which reveal any opening of the pack.

In the US, the difficult task of creating an automated *e-pedigree* system has been suggested, but it is not required by all States. The requirements that come closest to an automated e-pedigree system have been proposed by California. In March 2008, the California Board of Pharmacy (CBOP) published its "E-Pedigree Requirements" which are scheduled to go into effect in a phased approach between 2015 and 2017.

This changing regulatory environment is challenging the drug industry to take action and protect their products as thoroughly and effectively as possible.

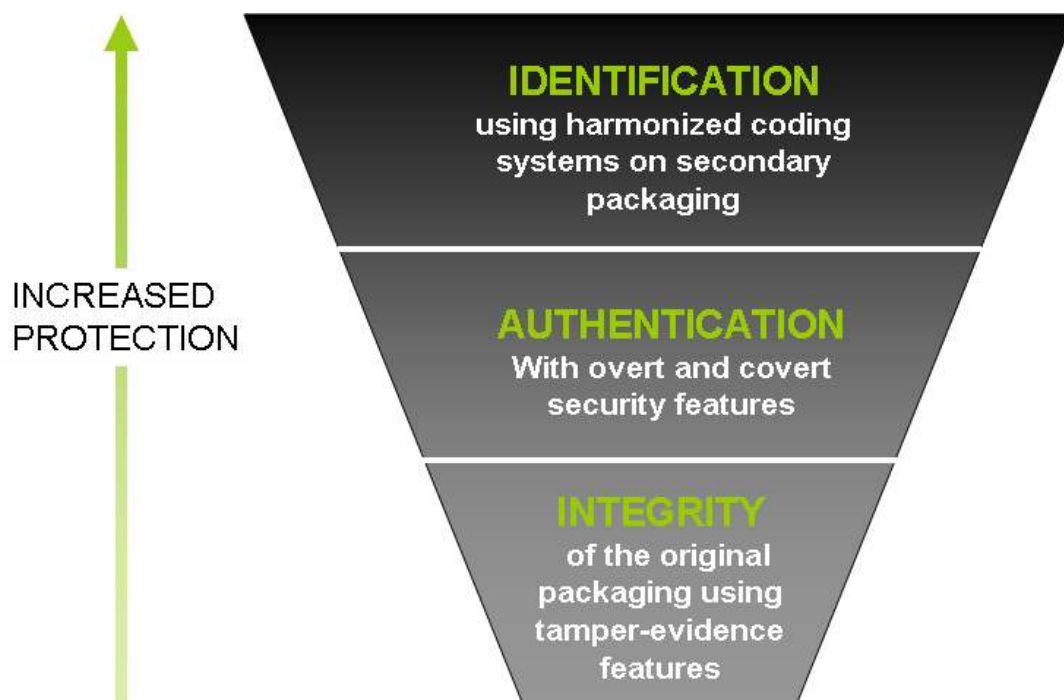
Country/State	Deadline	Serialization method
Argentina	15 Dec 2011	No recommendations. Preferred: 2D data matrix
Brasil	Jan 2012 (subject to change)	2D data matrix
Belgium	Current	2D data matrix and barcode
California (USA)	50% of drugs by 2015, 50% by 2016	E-pedigree, bar code, 2D data matrix, RFID
China	2015	Barcode
France	As per EU Directive with possible extension to 2022	2D data matrix
Germany	As per EU Directive; legislation by Jan 2013, enforced by 2016	2D data matrix
Greece	Ongoing	Bollini label barcode
India	Not applicable, only expiry date required	2D data matrix, RFID
Italy	Ongoing	Bollini label barcode (2D being discussed)
Russia	2016, current	Barcode
Spain	2016, pilot project finished	2D data matrix (pending)
Scandinavia	As per EU Directive	2D data matrix
Turkey	1 Jul 2009	2D data matrix
UK	As per EU Directive	2D data matrix
USA	2015-16 on some pharmaceuticals	E-pedigree, 2D as per GS1, eped (RF or barcode)

3. Current brand protection tools

An ideal anti-counterfeiting strategy might include the following features:

- Tamper-evident or tamper-resistant packaging
- Overt, covert or forensic authentication features
- Product identification at the unit level by harmonized coding standards

It would also be important for all medicines to be subject to the same level of security. The integration of safety features only on certain brands (e.g. high-risk medicines) might only move the threat to other medicines and therefore will not completely eradicate the problem of counterfeiting.



3.1 Tamper-Evident Seals

Tamper-evident packaging and tamper resistant closures are important features for ensuring brand integrity and patient safety. However, design features such as adhesive labels alone can not ensure the identification and authenticity of a drug. Furthermore, if a product are repackaged by third parties other than the original manufacturer, the effectiveness of any anti-counterfeit feature incorporated into the original packaging is seriously compromised.

3.2 Two-Dimensional Data Matrices

New standards based on 2D data matrix are being utilized to improve the traceability of medicines and ultimately increase consumer safety. The 2D data matrix can store drug information and should pose a challenge to counterfeiters by providing a method of safeguarding the origin and identity of a product. For example, Astrazeneca's "Serialized Authentication Program" was a two-pronged effort to protect drugs with unit-level serialized tamper-evident security seals combined with unique carton numbers (2D data matrix). The program has been used first to protect supplies of Nexium, a prescription-only gastrointestinal drug.

Data matrices can ensure product identification from point of manufacture to the pharmacy, allowing the authenticity of each unit dispensed to be verified before it reaches the patient. By identifying any duplication of data on drug packages at the point of dispensing, a pharmacist can be immediately alerted to the possible existence of a counterfeit product. Drug identification using the 2D data matrices also provides full visibility of product serialization information to be given to appropriate parties in the event of a recall.

3.3 Radio Frequency Identification (RFID)

After the Lipitor incident in 2003 involving 18 million tablets of potentially counterfeit Lipitor that had to be removed from distribution, Pfizer has been aggressively fighting counterfeiting by implementing a number of technologies on their products. In addition to color-shifting inks on several of their brands, including Lipitor, Zoloft, Norvasc and Celebrex, Pfizer is now shipping its most counterfeit-prone product, Viagra, with a label that contains both an RFID tag and a 2D barcode.

However, RFID has been limited by the development of standards around data exchange, numbering schemes and tag frequencies, and most drug companies have been reluctant to invest in the technology. In addition, the implementation of RFID in their supply chain affects many different departments within the industry, and it is quite costly to execute. Although the price of tags has come down somewhat, the implementation of the technology as a whole remains expensive. RFID is not an anti-counterfeiting technology, but it can be used as a way to track a drug's journey through the supply chain, or for medical compliance applications, or as a deterrent for stolen and diverted medicines.

3.4 Diffractive Optical Variable Image Devices

Pharmaceutical companies have taken the lead in using diffractive optical variable image devices (DOVID) for protecting their brands. Since GSK first used a tamper-evident hologram to seal packs of Zantac in 1989, these products have been widely used by the industry. Many drug companies use holograms such as labels, seals, hot-stamped patches, and blister-foils on their medicines.

The latest generation of holograms enables different motifs to be seen from different angles, or hologram strips printed in the back of blister packs. Blister packs constitute an important part of the packaging used for pharmaceutical products. There are several security features available to safeguard them and these are applied to the base material in a manner similar to that used for banknotes.



The ability of the hologram to provide effective protection lies in the continuous evolution of holographic techniques, which have succeeded at creating holograms that are easily recognized yet difficult to copy with 100% accuracy. The evolving role of the hologram has also been accompanied by increased use of this security device in combination with other authentication technologies. In such solutions, holograms can provide overt first-line authentication while covert features such as scrambled images, micro-text, UV-sensitive or other specialty inks provide second line authentication for trained examiners and appropriate decoding equipment.

4. A NEW CLASS OF MULTI-FUNCTIONAL LABELS

4.1 EN-TAG™ Product Overview

EN-TAG™ is a patent-protected, ultra-miniaturized data matrix technology that offers the highest level of security combined with high information content. By way of comparison, the information content of a single EN-TAG™ is over 100 times higher than that offered by a 2D data matrix. EN-TAG™ technology equips each product with a counterfeit-proof data carrier label for authentication and traceability purposes. It was designed to enhance the security features of reflective surfaces (e.g. holographic labels) by means of a digital read-only memory that can hold data such as text, pictures, videos, etc.

EN-TAG™ can be used as stand-alone labels or complemented with other overt or covert features for additional layers of security. EN-TAG™'s information content is highly secure. EN-TAG™ labels are fabricated with standard, low-cost materials approved for food and drug packaging. The manufacturing of the labels is aligned to a roll-to-roll process, as used in the hologram industry for the production of large numbers of identical labels. The high-precision laser marker for the direct writing of individual tags can be customized and inserted in a continuous label production line.

4.2 Thermal Monitoring

As an add-on benefit, EN-TAG™ can also be used as a thermal monitoring feature to verify the correct state of preservation of drugs and biologics *at the unit level* (caps, blisters etc.). This is achieved by integrating EN-TAG™ with a proprietary, thermo-sensitive polymeric layer (T-TAG). Thermal monitoring of drugs is then made possible by detecting subtle optical changes when the tag is exposed to temperatures exceeding a pre-set threshold. Threshold temperatures are fully customizable to specific temperature requirements. Most importantly, exposing EN-TAG™ to above-threshold temperatures does not affect the quality of the encoded information.



EN-TAG™ on secondary packaging

4.3 Features

- **Flexibility.** EN-TAG™ micro-labels can be integrated into any security hologram or otherwise reflective surface (e.g. metallic foils) with flexible sizes ranging between 1-10 mm depending on information content requirements.
- **Robustness.** Suitable for temperatures up to 80°C. Also robust to wear and tear, accidental or intentional scratching.
- **Size.** Storage capacity for a data volume of up to 30 kB per cm². For example, a 1 mm² tag may contain ~300 text characters.
- **Content.** Storage data may include logos, videos or drug pedigree data in any language, such as drug name, dosage form, strength, expiration date, lot number, etc.
- **Security.** Barely visible to the naked eye (covert). The tag provides protection against unauthorized access to the data and no susceptibility to manipulation thanks to encryption.
- **Cost.** Low cost solution and suitable for use with products manufactured in large quantities (mass production)
- **Sensing Functionality.** Standard bar codes or holograms contain no sensing functionality. Sensing tags (chemical indicators) with “yes or no” response to temperature exposure exist and are heavily patented, but they do not integrate the time and do not store information. EN-TAG™ can monitor the thermal history of your product.
- **Optically readable.** EN-TAG™ labels are optically readable thanks to an advanced nano-patterning technology and proprietary software. Information content can be read with an inexpensive reader and/or cell phones featuring a suitable camera (minimum 5MB).
- **Speed-to-market.** EN-TAG™ technology is ready for batch production. For in-house serialization applications, simple factory integration of our printing devices is all that is needed to implement a global solution.



4.4 Content and Format

A single EN-TAG™ may contain multiple elements of e-pedigree information (text) as well as digital images (e.g. company logo) and video files. The specific information content of the EN-TAG™ may be chosen to follow EFPIA's recommendations for coding of pharmaceutical products derived from the GS1 Data Matrix standard:

- Manufacturer Product Code (GTIN or NTIN): 14 digits
- Batch Number: up to 20 alpha-numeric characters
- Expiry Date: 6 digits (YYMMDD)
- Unique Serial Number (randomized): up to 20 alpha-numeric characters



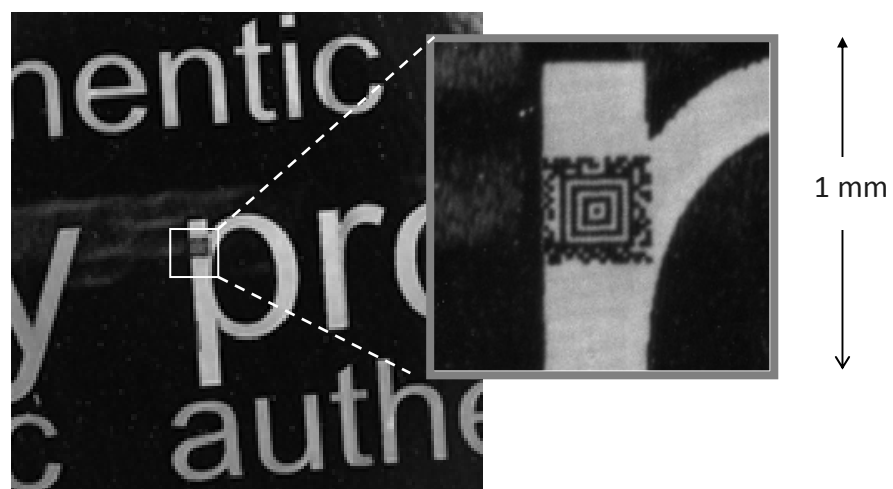
Example of EN-TAG™ with encoded information

The amount of information that can be securely stored on the EN-TAG™ depends on its dimensions. The larger the EN-TAG™, the more information can be encrypted. By way of example, a 1x1 mm tag contains approximately 0.3 kB of information (~300 text characters). A larger 9x9 mm tag can contain over 22 kB of information (~27,600 text characters)!

4.5 Benefits

EN-TAG™ technology is ready for batch production and offers a number of benefits and advantages to pharmaceutical manufacturers:

- By comparison with conventional security features, EN-TAG™ meets all of the requirements outlined above: absolute security, true authentication and identification.
- Proprietary, patent-protected technology.
- Suitable for the mass market, since production by means of printing makes it practical even for large batches. EN-TAG™ can be easily applied to the secondary or primary packaging, e.g. on cardboard boxes, blisters or vials.
- Laser printing and optical reading customizable on-demand for product serialization purposes.
- Less expensive or as expensive as other security features, including bar codes.
- First-in-class security feature to monitor the thermal history of temperature-sensitive drugs such as biologics, vaccines, etc.
- Empowers consumers to check for themselves the authenticity and temperature history of their drugs. This connection establishes trust among consumers and manufacturers.



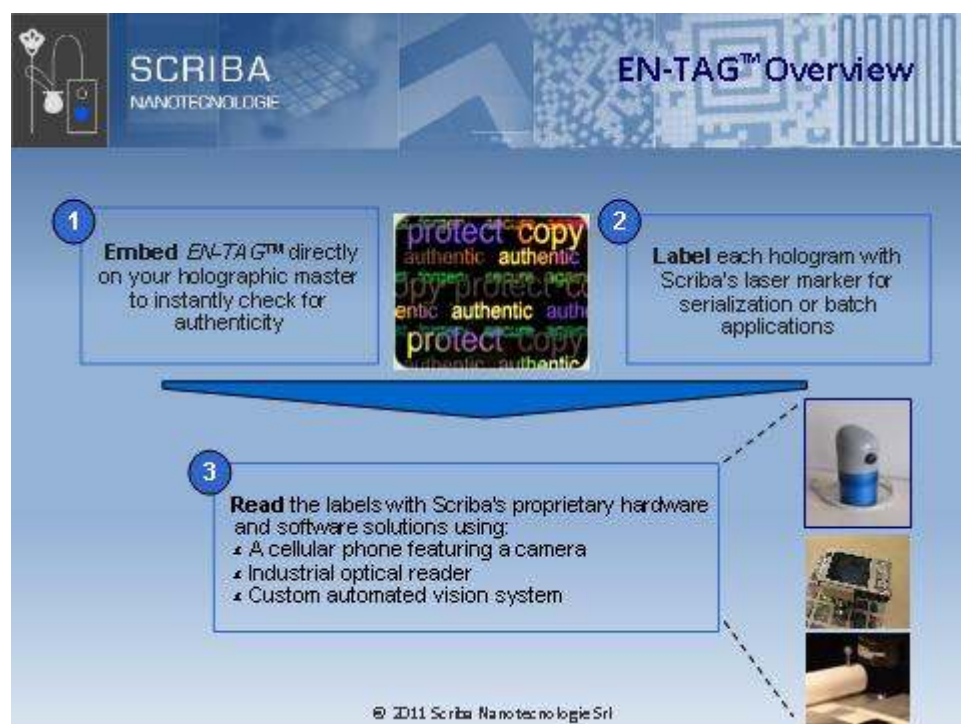
EN-TAG™ on holographic substrate

4.6. Integration Process

EN-TAG™ is a proprietary technology comprising all components required for counterfeit protection and effective product authentication: coding software, laser printer and portable and/or in-line reading devices. The entire production of EN-TAG™ security labels may take place either on-site or at Scriba's. For on-site applications, factory integration of our printing devices is all that is required. Alternatively, Scriba can deliver the inscribed labels directly to you, quality controlled and ready to be applied to the products.

The process of embedding EN-TAG™ onto an existing hologram is straightforward and can be summarized as follows:

- **Embed** EN-TAG™ directly on your holographic master to instantly check for authenticity
- **Label** each hologram with Scriba's laser marker for serialization or batch applications
- **Read** the labels with Scriba's proprietary hardware and software solutions using:
 - A cellular phone featuring a camera
 - Industrial optical reader
 - Custom automated vision system



5. Conclusion

The holographic industry is continually evolving and working hard to destroy the myth that sophisticated holograms cannot be counterfeited. The evolving role of holograms lies in their ability to combine authentication with detection, which is the reason why some of the largest pharmaceutical companies have recognized the need to make holograms an integral part of their anti-counterfeiting strategies.

The EN-TAG™ technology meets the ever increasing need to ensure that our drugs are safe and authentic. For the pharmaceutical manufacturer, highly secure packages or blister packs deter counterfeiters, offer protection against unjustified claims for product liability and fulfill a marketing function.

EN-TAG™ technology is totally unique and innovative. The ability to conceal product information in a secure fashion represents a competitive edge that never goes away in this industry.

6. Strategic Partnerships

At Scriba, we feel that there is a solution to any problem. The globalization and changing regulations of the industry in particular are challenging us to stay abreast of new developments, regulations and technologies. Our problem-solving expertise and technical know-how make Scriba the ideal partner for the development of new and improved security solutions.

If you would like to know more about EN-TAG™, please do not hesitate to contact:

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