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Track & Trace for Pharmaceutical Applications

GENERAL INFORMATION

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Contents

1. Scope

Counterfeiting of pharmaceutical products is not often discussed by manufacturers, for obvious reasons, but currently it is:

- Increasing at an alarming rate
- Very lucrative, with low penalties
- A significant danger to patients worldwide

Counterfeiting is difficult to control (and sometimes to detect), and is growing increasingly sophisticated.

Counterfeit medicines have four main categories:

I. Appropriate amount of active ingredient - the perfect imitation of a preparation with the same active ingredients and identical packaging. From a medical point of view, the risk associated with this is small, assuming that the quality of the preparations is correct. However, with any counterfeit medicine there is no guarantee of the manufacturing process standards with unknown impurities common.

II. Some active ingredient - counterfeit medicines available in packaging identical to that of a trademarked product. In general, these products contain the active ingredient stated, however, its quality is often poor and the quantities may be insufficient. The consequences of this are lack of efficacy and in the case of antibiotics may lead to the development of resistances by pathogens.

III. No active ingredient - a product that looks like a genuine medicine but contains no active ingredient. In such cases, the patient's condition will neither be cured nor will any pain be alleviated.

IV. Harmful ingredients - the counterfeit medicine contains harmful or poisonous substances.

WHO (World Health Organisation) estimates that at present, 8% of drugs globally are counterfeit, with this percentage rising to 65% in developing countries. The international drug counterfeiting market is currently at valued at $40bn, estimated to rise to $75bn by the end of 2010.

Measures to impede the success of counterfeiting of medicines generally comprise of five separate objectives:

- Add at least one overt and one covert feature to all primary packaging;
- Add overt and covert features to secondary packages where applicable;
- Upgrade covert technologies to invisible encrypted graphics for all printed components;
- Develop and implement traceability technology on all priority packs using some form of mass serialization technique to create and place unique serial identification on each pack;
- Add tamper evidence to the pack.

The purpose of this paper is to inform about the various techniques being developed for mass serialisation of pharmaceutical packs at the unit-of-sale level and the application of Track and Trace technology and anti-counterfeiting tools. The other advantages of such a scheme will also be discussed.

2. Track & Trace Basics

2.1. An Evolving Compliance Landscape

The compliance landscape has been evolving for some period now. As governments and legislators have become more aware of the problems of counterfeit drugs, they have sought to protect their citizens by introducing measures to combat the counterfeiters. This has led to a number of different solutions being discussed and implemented. For the purposes of this paper, the focus is on the differences between the US Electronic Pedigree (ePedigree) based approach and the European style Mass Serialization route. Understanding where these approaches come from helps put the differences in perspective. More critically it highlights where these approaches converge.

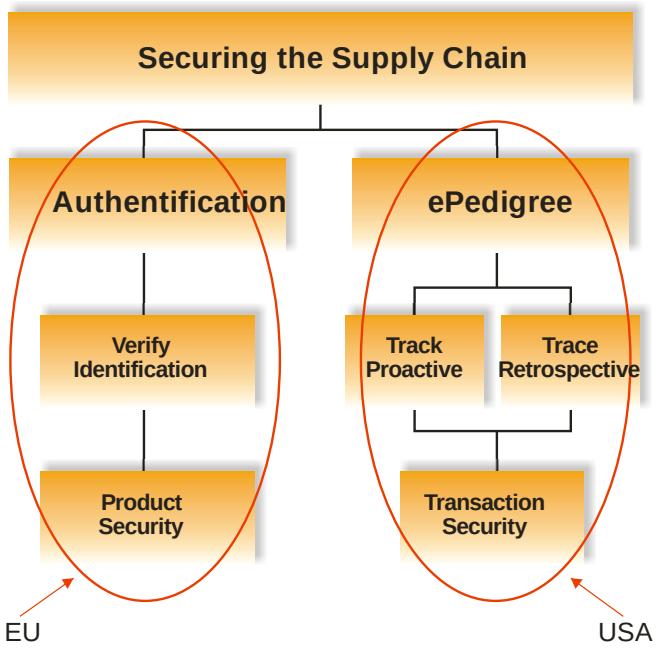


Figure 1 - Varying Serialisation Approaches

2.2. The Theory of Track & Trace

In distribution and logistics of many types of products, track and trace or tracking and tracing, concerns a process of determining the current and past locations (and other information) of a unique item or property.

The arrival or departure of the object is observed and the identification of the object, the location where it was observed, the time, and the status is recorded.

It is then the task of the system to collate this information and other information obtained at various locations and at various times into a coherent pattern detailing the movement of the object.

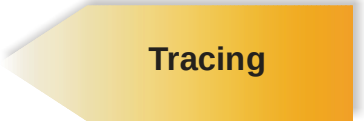
It is often said that we track objects forwards, in a proactive manner, while we trace products backwards in a retrospective manner.

Tracking within the supply chain offers:

- Control of distribution channels
- Recall Management
- Stock Management (Expire Date)
- **Anti Counterfeit** (brand protection)

Tracing offers:

- Origin of Product



- which includes **Authentication**

It would be of great benefit in the fight against pharmaceutical counterfeiting if a full track and trace system could be implemented. However, such and implementation for the very complex supply chain of pharmaceuticals world-wide is a task of daunting magnitude. Two major schemes have arisen for the control of pharmaceutical products; these are the American ePedigree and the European EFPIA (European Federation of Pharmaceutical Industries and Associations proposals.

2.2.1. The ePedigree

A system which is dependant on track and trace concepts is the ePedigree being introduced in the USA as an anti-counterfeiting tools and a check against reimbursement fraud for pharmaceutical products.

There already exists a number of paper based pedigree schemes in the USA today. Manufacturers and wholesalers give their clients access to websites from which these pedigrees, in PDF format, can be downloaded. Those documents are then used to create a new 'outbound' pedigree for the next company in the drug supply chain.

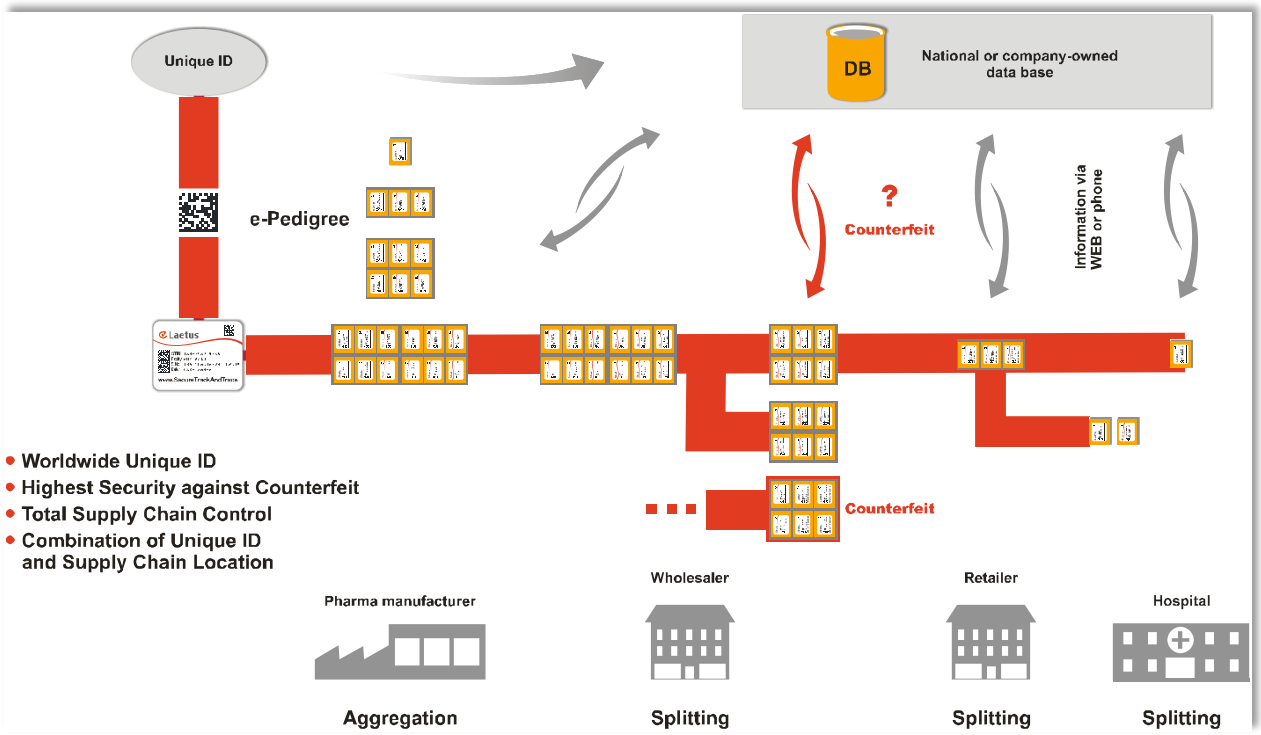


Figure 2 – Principal of ePedigree

Since all of the pedigree documents provided are not re-usable, companies must transpose the data from the inbound pedigree to the outbound pedigree they are going to provide. This is a labour intensive step for most companies with mistakes being made and original information being dropped from the inbound pedigree.

ePedigree is based around creating a non-reputable electronic record surrounding chain of custody and chain of ownership (sale) of prescription medicines and medical devices within the supply chain. It contains information on all transactions from the time a pack or logistics unit leaves the manufacturer to the point it enters a pharmacy or someone dispenses the drug. Encompassing the entire shipping and wholesale process, it critically includes wholesalers who may be responsible for repackaging into other unit levels e.g. from pallet to case.

Although an open ePedigree standard is ratified, the USA are some way from its adoption. This has resulted in revised legislation that states any manufacturer selling drugs in California must have an ePedigree for 50 per cent of its products by the start of 2015. The remaining 50 per cent must be designated an ePedigree before 1 January 2016.

Another wave of legislation comes into affect on 1 July 2016 prohibiting wholesalers or re-packagers from selling, trading, or transferring a dangerous drug without a pedigree. Also they cannot acquire a dangerous drug without receiving a pedigree.

The complete legislation will finally be implemented on 1 July 2017, when the measures affecting pharmacies come into force. These will then also apply to the wholesaler and re-packager regulations implemented in 2016 to the pharmacies.

Characteristics of the California ePedigree

- It is fully electronic (it is not paper-based) - The law and all of the discussion of the law by the Board of Pharmacy make it clear that the only acceptable form of a pedigree is electronic. This will make it much more reasonable to implement because supply chain members can make use solely of computers to exchange, store and validate pedigrees, without fear that their trading partners can only handle paper pedigrees.
- Pharmacy returns must be reflected on pedigrees - This was an original requirement of the Florida Pedigree Law too, but it was removed under pressure from lobbyists before the law went into effect. So far, it remains intact in California, but the law is not yet in effect. What it means is that when a pharmacy buys drugs from someone and they return those drugs, regardless of how little time has transpired, they must provide a pedigree update so that subsequent buyers of those drugs can see their purchase, and return transactions.
- It starts with the manufacturer - In Florida the first wholesaler started the pedigree. In California, the pedigree must be started by the manufacturer or it is not valid. Currently, in States like Florida, the pedigree starts with the first point of distribution, which in older FDA thinking was the first point of vulnerability of the drug.
- It requires item-level serialization - California is very clear that they consider the concepts of 'electronic track and trace' and 'item-level serialization' as being inseparable. That is, if you have one but not the other, then you don't have a pedigree system. Every drug package must have a USC[1] on it, applied by the manufacturer or re-packager, and that SNI must be included in the pedigree (the electronic record). This is a substantial difference from the Florida law which has no such requirement. Individual SNI's are assigned at the product pack level and become an intrinsic part of the pedigree.

2.2.2. USA Guidance for Industry Standards

On March 29th 2010 the FDA published the final version of the 'Guidance for Industry Standards for Securing the Drug Supply Chain - Standardised Numerical Identification for Prescription Drug Packages'.

It describes the following procedure for item-level serialization.

The SNI[2] for most prescription drug packages should be a serialized National Drug Code (sNDC). The sNDC is composed of the National Drug Code (NDC) (as set forth in 21 CFR Part 207) that corresponds to the specific drug product (including the particular package configuration) combined with a unique serial number, generated by the manufacturer or re-packager for each individual package.

Serial numbers should be numeric (numbers) or alphanumeric (include letters and/or numbers) and should have no more than 20 characters (letters and/or numbers). An example is shown below with a 10-character NDC.

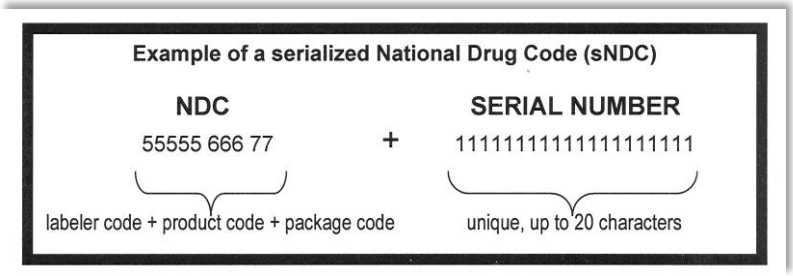


Figure 3 - FDA FINAL Guidance

[1] *Unique Serial Code refers to random non-predictive codes used as the serialisation component*
[2] *Standardised Numerical Identification*

Expiration date and/or lot or batch numbers are not part of the recommended SNI. Expiration date and/or lot or batch numbers are already accessible because FDA regulations require the inclusion of this information on the label of each drug product[3].

In addition, the SNI can be linked to databases containing this and other information. Addition of this information within the SNI will unnecessarily increase the length of, and introduce complexity into, the SNI. However, if a manufacturer or re-packager chooses to include expiration date and/or lot or batch number with the SNI, it should ensure that the resulting number still permits users to distinguish and make use of the SNI.

For example, expiration date and lot or batch number may be incorporated in accordance with the GS1 standards for use of Global Trade Item Numbers (GTIN).

2.2.3. The European EFPIA End To End Scheme

In May of 2007, The European Federation of Pharmaceutical Industries and Associations (EFPIA) issued a guidance document entitled 'Packaging Standard for Counterfeit Resistant Packaging and its Implementation into International Supply Chains in Europe'.

The EFPIA serialisation concept aims to establish a common standard for product coding in Europe (rather than having 27 different national code systems) and to increase traceability across the supply chain. The EFPIA code will use a Data Matrix based on the EAN.UCC (GS1) standard using an international syntax. The code is very robust in reading and can be applied with rather little extra costs by variable printing technologies. However, the emphasis here is not on the generation of a Pedigree scheme, but to generate product security by identification of only the products origin and not its passage through the supply chain.

Mass Serialization is about allocating a unique serial number to all products at the item level - sometimes referred to as a UID (unique identification). Traditionally, numbers or identifying codes would be sequential, but as part of an anti-counterfeiting initiative this is inadequate. Sequential serial numbers can easily be predicted by counterfeiters and replicated along with batch / lot codes and expiration dates. Therefore a mechanism needs to be in place to allocate random numbers so they are non-predictable.

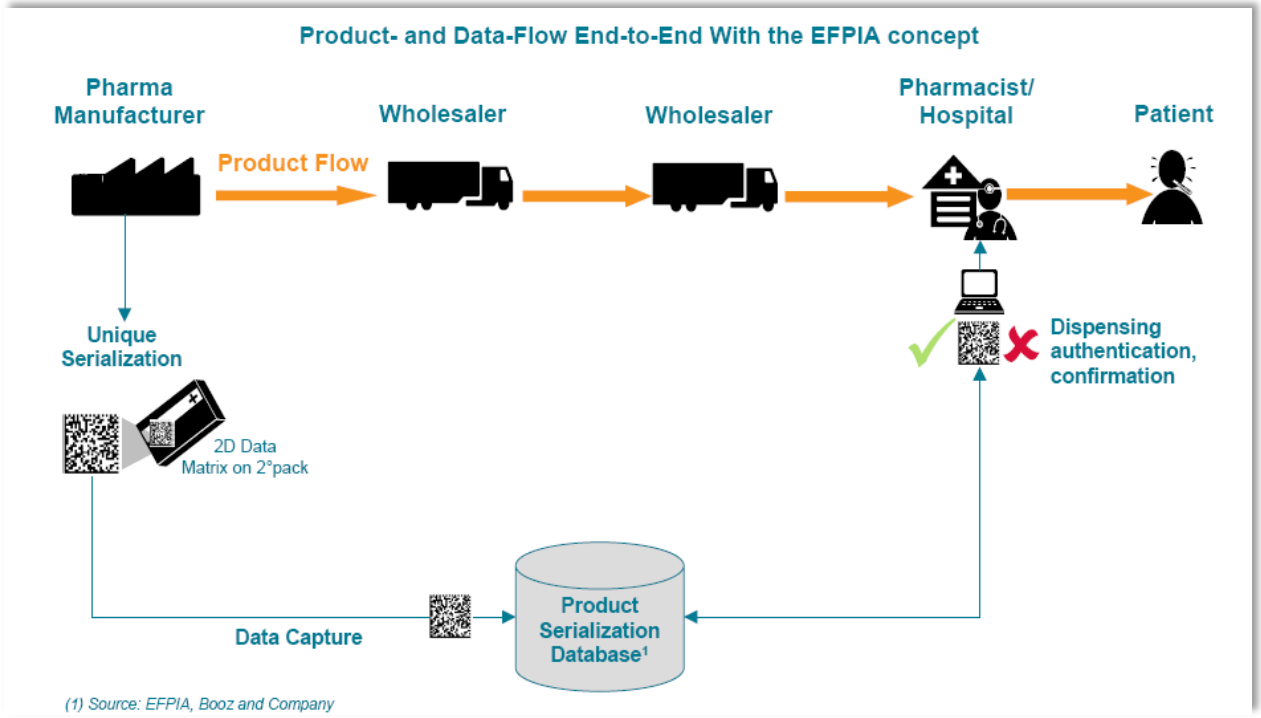


Figure 4 – EFPIA Scheme

[3] *See 21 CFR 201.17, 201.18, 211.130, 211.137, 610.60, and 610.61.*

EFPIA recommendations

As a first step towards securing the supply chain, a 'bookend' strategy will be employed where product is serialised at the point of manufacture and checked at the point of dispensing. This gives rise to the possibility that a drug authentication scheme will happen that does not involve all the trading partners in the supply chain.

Instead, the pharmaceutical manufacturers and the hospitals and pharmacies that dispense the medications will adopt a relatively simple scheme of this bookend drug authentication. This would be driven by the manufacturers by the threat of liability in the event of counterfeit medication appearing in the supply chain.

A Pharmaceutical Interchange Logistics Link (PILL) Database will allow security checks and also allow reimbursement data for governmental tax surveillance programs. The data segregation will be handled by a central database system, generated by the manufacturer, linking back to the respective company database. The system requires that the pharmaceutical manufacturer installs adequate printing systems within their packaging lines, whereas the pharmacies need to be equipped with 2D bar code readers.

It's a process that is similar to what happens today when making a credit card transaction: your card is swiped, the information is entered into a database and crosschecked to determine whether the card number is valid and an authorisation or rejection is delivered.

With mass serialisation, if one of more duplicates of the same serial number are dispensed, a red flag can be raised alerting drug makers to potential counterfeits or diverted product in the supply chain. In addition, mass serialisation will be combined with overt, covert and forensic security features for higher levels of pharmaceutical security and a means to conduct rapid follow-up investigations.

So mass serialization in Europe should be a reality over the next 2-3 years, reinforcing the need for a unique standard for adoption in Europe in order to ensure the introduction of an efficient and cost effective system

Data Matrix Bar code and human readable have unique non-predictive serial identity and other relevant data on each carton.

A closer look at the EFPIA code

The suggested code is a GS1 Data Matrix code and contains four elements of information, i.e. article number, batch number, expiry date and a randomised serial number.

- Manufacturer Product Code - GTIN [or Pseudo GTIN e.g. CIP code] 'Global Trade Item Number' according to GS1 Standards (14 numeric digits)
- Unique serial number (randomized – up to 20 alpha-numeric characters)
- Expiry date (6 digits – YYMMDD)
- Batch number (up to 20 alpha-numeric characters)

Figure 5 – EFPIA Coding

The combination of article and serial number provides the pack's unique identity. The exact form of the information included in the Data Matrix code follows the GS1 Data Matrix standard and is described in the EFPIA 'European Pack Coding Guidelines. An example of a Data Matrix code is shown in Figure 5.

3. Benefits of Track & Trace

With unit-of- sale serialisation, the Product code (GTIN), batch number additional USC and expiry date will need to be included in a Bar code in order to be read automatically. This then gives the following advantages:

3.1. Automatic Detection of Expired Products

Expired products that are either returned or expire in warehouses are the bane of pharmaceutical distributors. With serialisation, distributors obtain more visibility into their warehouses and potentially into their customers' inventory management practices. With improved visibility into distributors' warehouses, manufacturers can balance their inventory across their distributors, an area of untapped opportunities. Serialisation can significantly reduce the industry's losses due to expirations.

A potential health risk is the sale of outdated drugs. The problem in Turkey for example is that pharmacies usually cannot return stocks to wholesalers as they are in other Countries. Therefore there is a temptation to keep selling drugs that have passed the expiration date. A sting operation in 15 warehouses found a truck full of outdated medicines used for leukaemia treatment and two trucks which were full of out-of-date medicines used for cancer treatment[4]. By the use of serialisation, manufacturers are able to set specific batches into an 'expired' state and the hospital or pharmacy will be informed of this when they check the product.

3.2. Brand Protection

Brand protection is paramount for drug manufacturers, and for good reason. A single product-tampering incident can wreak long-term havoc on a company's reputation. Past cases of product tampering show that it can take months, if not years, for a compromised product to recover market share, requiring significant investments in marketing and public relations to do so. Because serialisation tracks the pedigree of each product, it significantly reduces the chances of tampering, thereby adding a valuable protective layer.

3.3. Prevent Counterfeits

Counterfeiting is difficult to control (and sometimes to detect), and is growing increasingly sophisticated. The biggest issue of counterfeit medicines must be consumer safety. In July 2005, Pfizer recalled a batch of Lipitor 20mg tablets due to the discovery of counterfeit packs in the legitimate supply chain. A further Class 2 recall was initiated by the MHRA in July 2006, when further samples of the same lot were discovered in the supply chain. In 2008, there were at least 651 different types of counterfeit branded, generic and over-the-counter drugs detected and with improved appearance and packaging have made these fake goods even harder to detect[5]. Linked to the patient safety issue are the significant threats to the company's brand protection, and potential product liability actions.

Securing the pharmaceutical supply chain and products is a challenging task. As varied as the threat itself are the means available to provide protection-for the consumer as well as the manufacturer. The key to a successful security strategy is a careful risk analysis, followed by the cross-functional development and implementation of an integrated anti-counterfeiting strategy. The implementation of an efficient technological anti-counterfeiting strategy requires the following three principles:

- The use of tamper-evidence packaging on all products in order to guarantee the integrity of the packaging content.
- An individual choice of overt, covert and forensic authentication features, such as colour-shifting inks, holograms, taggants should secure for high risk products.

[4] *Source: http://www.internethaber.com/news _detail .php?id=73650, March 13, 2007*
[5] *Data provided by the Pharmaceutical Security Institute (PSI)*

- The introduction of a harmonised and standardised serialisation coding system to allow a comprehensive surveillance of the pharmaceutical distribution chain.

The implementation of authentication technologies by specialised and security certified system integrators and packaging specialists leverage the best techniques and technologies currently available to deter, detect and avoid the criminal practices that jeopardise human lives and erode legitimate earnings.

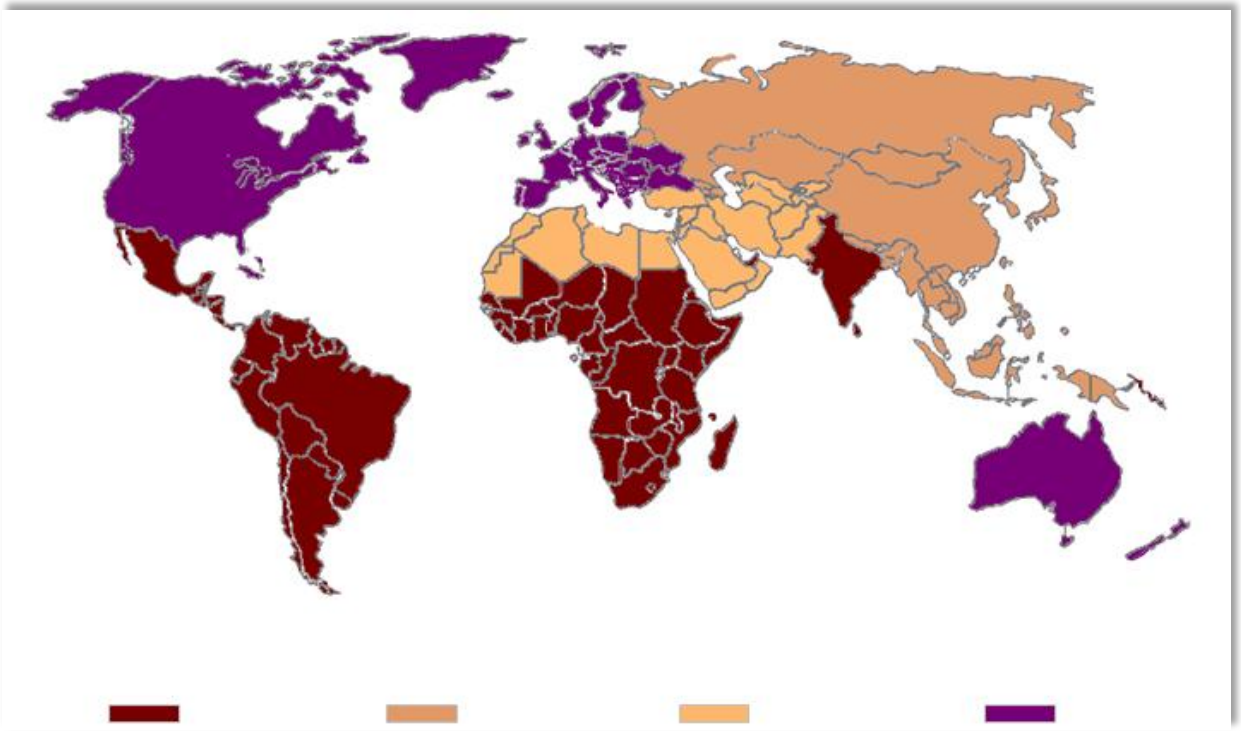


Figure 6 - Counterfeit products in Pharmaceutical Market [6]

3.4. Fight Reimbursement Fraud

All countries require market authorization for pharmaceuticals to be sold and most countries have a national plan defining which pharmaceuticals can be reimbursed. One thing that is driving Europe's adoption of serialisation is how they process medical reimbursements through their healthcare systems. Consumers submit documentation about the drugs they purchase to the country's healthcare agency, which then provides reimbursement. Turkey[7] took a leading role in addressing fraud in the reimbursement process by mandating new drug traceability processes. So the motivation to drive this serialisation process forward in many countries is tied to management of fraud in the reimbursement process, as well as patient safety.

3.5. Enable Partial Recalls, Prevention of dispensing Recalled Product

A drug recall removes a prescription or over-the-counter drug from the market. In the event of a recall, the regulatory authority or the manufacturer has the responsibility to notify all pharmacies and locations that have the product in question. Drugs may be recalled for a number of reasons, incorrect manufacturing or contamination is detected by the manufacturer, and unwanted side effects are reported to the regulatory authority.

[6] *Source: Pharmaceutical Packaging And Labelling Summit, Amsterdam 2011, Kraehenbuehl*
[7] *Turkish reimbursement fraud is estimated to cost Turkey around $150m a year*

Currently it is only possible to recall by complete batch, which may result in many thousands of packs of drugs being recalled. In some cases it may be desired to only recall a portion of the batch and this becomes a possibility.

Additionally by the use of serialisation, manufacturers are able to set specific batches into a 'recalled' state and the hospital or pharmacy will be informed of this when they check the product. This will prevent recalled medicines from being dispensed.

3.6. Avoid General Dispensing Errors

By providing all the required information pertaining to the drug product in question it is possible to therefore prevent dispensing errors at the pharmacy and hospital.

4. The Technology of Pack Marking

Currently there are five major ways of marking or printing packs with the required data, please note that the technologies of marking and printing are separate ones yet often confused.

- **Marking** – This is the operation of leaving a visible trace or impression on a surface. This can be by adding to or removing material from that surface, or by modifying the surface contours.
- **Printing** - This is a process for reproducing both text and images, typically by applying ink onto paper or another substrate capable of retaining it.

The majority of techniques for mass serialisation are referred to as 'pack marking', although they often work by printing ink onto the pack. One technique Laser ablation[8] involves the removal of material from the surface of the pack, leaving a lighter coloured substrate visible underneath.

It has to be stated, that there is not any individual Auto ID technology predestined for serialisation or Track & Trace. The selection of the Auto-ID technique depends on the application and there must be the clear message, that all of them can be used and combined. It much more important to standardise for the data structure used in the various data carriers (see 4.4).

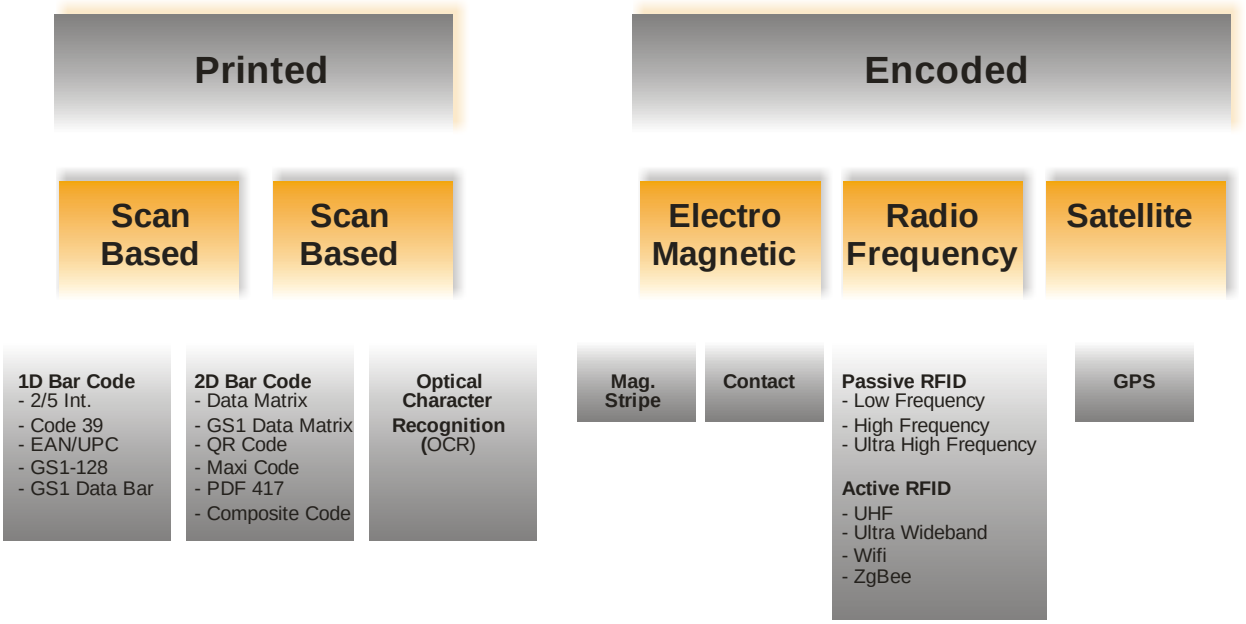


Figure 7 – Type of Auto-ID Technology

4.1. Data Carrier for Pack Marking

Much has been written about the relative merits of RFID and Bar codes as data carriers for the new implementation of pharmaceutical pack serialisation. Initially[9] in 2004 the FDA was recommending RFID as the technology of the future of pack serialisation with an adoption date of 2007. Later they took a less aggressive stance on the matter. The situation today is that all groups are considering bar codes as the technology for today with RFID still evolving.

Evaluating the new RFID technology and how it compares with current bar coding technology is interesting. Bar codes are well understood at this point and their challenges have long been addressed, although certain questions over code grading still remain with the comparatively new Data Matrix codes.

[8] *This means removal of material from the surface of an object by vaporization, chipping, or other erosive processes*

[9] *http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108372.htm*

While bar code labels are inexpensive, widely used, and based on open standards, they present the disadvantages of having a line-of-sight requirement; some constraints of static data; and the problems caused by inconsistent marking quality.

RFID tags do not require a line of sight, which eliminates the need to orientate and present products correctly to the scanner, multiple packs may have been collated in a larger packaging unit and then have their data collected. RFID tags have a longer read range and outperform bar codes in adverse physical conditions. Also, the volume of data that RFID tags provide can lead to raised operational efficiency and greater product visibility.

However, RFID is more expensive than bar code technology; RFID standards are still evolving; and physical limitations, such as interference, can affect RFID performance.

Systems and RFID tags that allow changes to the stored data have both negative and positive connotations. The positive is because this allows flexibility in the data contained; the negative side is because of the chance of tags becoming compromised. Various security vulnerabilities have been highlighted with these tags.

The interest in RFID chips has waned significantly among pharmaceutical manufacturers. A recent study by IDC Health Industry Insights[10] in the USA entitled 'Health Industry Insights 2009 Leading Indicators in Life Science IT Spending Survey 2Q09' supports this assertion.

However, it is important to state that both RFID and Bar codes should only be thought of as data carriers and the underlying mechanism of handling this data is the important consideration.

4.1.1. Linear Bar Codes

Linear Bar codes became established in the late 1970's, being printed on small labels and applied to supermarket goods. The first successful bar code was the American Universal Product Code (UPC) which enabled the code to be read from either direction and still decode as the correct value.

Linear symbologies are optimised to be read by a laser scanner, which sweeps a beam of light across the bar code in a straight line, reading a slice of the bar code light-dark patterns.

Some symbologies use interleaving. The first character is encoded using black bars of varying width. The second character is then encoded, by varying the width of the white spaces between these bars. Thus characters are encoded in pairs over the same section of the bar code. Interleaved 2 of 5 is an example of this. Other codes are modular in design, for example in UPC code each of the numbers shown underneath the Bar code will be represented by 2 bars or varying widths and the spaced distance between these 2 bars.

Figure 8 – UPC-A Symbol

Figure 8 shows an example of a GTIN-12 number encoded in UPC-A bar code symbol. The first and last digit are always placed outside the symbol to indicate quiet zones that are necessary for bar code scanners to work properly. There are currently about 50 types of linear Bar codes in operation today.

[10] *http://www.pharmamanufacturing.com/articles/2010/033.html*

Bar Code View	Related Standards
EAN / UPC 	Symbology specified by ISO/IEC 15420
Code 39 	Symbology specified by ISO/IEC 16388
Code 32 	Based on Code 39, fixed structure and specific decoding algorithm
PZN Code 	Based on Code 39, fixed structure specified by IFA GmbH
Code 2/5 Interleaved 	Symbology specified by ISO/IEC 16390
GS1- 128 	Symbology specified by ISO/IEC 15417 Data structure conform to GS1 General Specification V 11.0

Table 1 – Overview of Most Popular 1D Bar Code

As mix up between linear and stacked bar code the GS1 Data Bar family was developed to offer the readability by linear scanning (laser based) systems. In Reality those code need an imaging system for reading as well.

Bar Code View	Related Standards
GS1 Data Bar Limited 	Symbology specified by ISO/IEC 24724 (formerly RSS)
GS1 DataBar Stacked 	Symbology specified by ISO/IEC 24724 (formerly RSS)

Table 2 – Extract from GS1 Data Bar Code

4.1.2. Stacked Bar Codes

The first type of two dimensional Bar code was the Stacked code. Stacked bar codes were developed in the early 1980s to encode more data in a smaller footprint than allowed by the then current linear bar codes. Today, the primary advantage to using a stacked symbology is to encode more data into a symbol that can still be read by a conventional laser bar code scanner.

One significant drawback to stacked symbologies is their sensitivity to scanner tilt. To decode the symbol, the laser beam must be aligned so that the beam passes through the rows one at a time. The stacked symbology PDF417 provides the user with a little more tolerance. Since PDF417 has three different encoding schemes that read every three rows, the laser beam can pass through up to three rows at a time and still decode the symbol.

Bar Code View	Related Standards
PDF 417 	Symbology conform to ISO/IEC 15438
Micro PDF 	AIM Symbology Specification MicroPDF417
Composite Symbology® (GS1) 	Symbology conform to ISO/IEC 24723 (only in combination with GS1 1D or with GS1 DataBar code)

Figure 9 – Extract from Stacked Bar Code

4.1.3. Two Dimensional Bar Codes

Two-dimensional bar codes were developed in the late 1980s to store larger amounts of information with high security, in a limited space. While matrix codes are much more space efficient and offer increased data capacity than stacked 2D codes, matrix codes must be read with a two dimensional camera-based reader. The most popular code in use today is Data Matrix. Originally developed by a NASA engineer for marking and tracking space shuttle parts, the symbol was introduced into the public domain in 1995, and the AIM standard released in 1996. Data Matrix offers the robust Reed-Solomon method of error correction and has no orientation requirements. It has therefore become the data carrier of choice for Track and Trace applications.

Bar Code Look	Related Standards
Data Matrix ECC 200 	Symbology specified by ISO/IEC 16022
GS1 Data Matrix 	Symbology specified by ISO/IEC 16022 Data structure conform to GS1 General Specification V 11.0
QR Code 	Symbology specified by ISO/IEC 18004
PPN Data Matrix 	Symbology specified by ISO/IEC 16022 Data Structures conform to ISO/IEC 15418 (ANSI MH10.8.2)

Figure 10 – Extract from 2D Bar Code

Figure 11 – Data Matrix Code

4.1.4. Radio Frequency Identification (RFID)

The 1980s became the decade for full implementation of RFID technology, though interests developed somewhat differently in various parts of the world. The greatest interests in the United States were for transportation, personnel access, and, to a lesser extent, animals. In Europe, the greatest interests were for short-range systems for animals, industrial, business applications and toll roads in Italy, France, Spain, Portugal, and Norway were equipped with RFID. A key to the rapid expansion of RFID applications was the development of the personal computer (PC) that allowed convenient and economical collection and management of data from RFID systems.

Interest was also keen for RFID applications in Europe during the 1990s. Both microwave and inductive technologies were finding use for toll collection, access control, and a wide variety of other applications in commerce. Here is a synopsis of the major technologies available today.

There are generally three types of RFID tags: active RFID tags, which contain a battery and can transmit signals autonomously, passive RFID tags, which have no battery and require an external source to provoke signal transmission, and battery assisted passive (BAP) RFID tags, which require an external source to wake up but have significant higher forward link capability providing greater range.

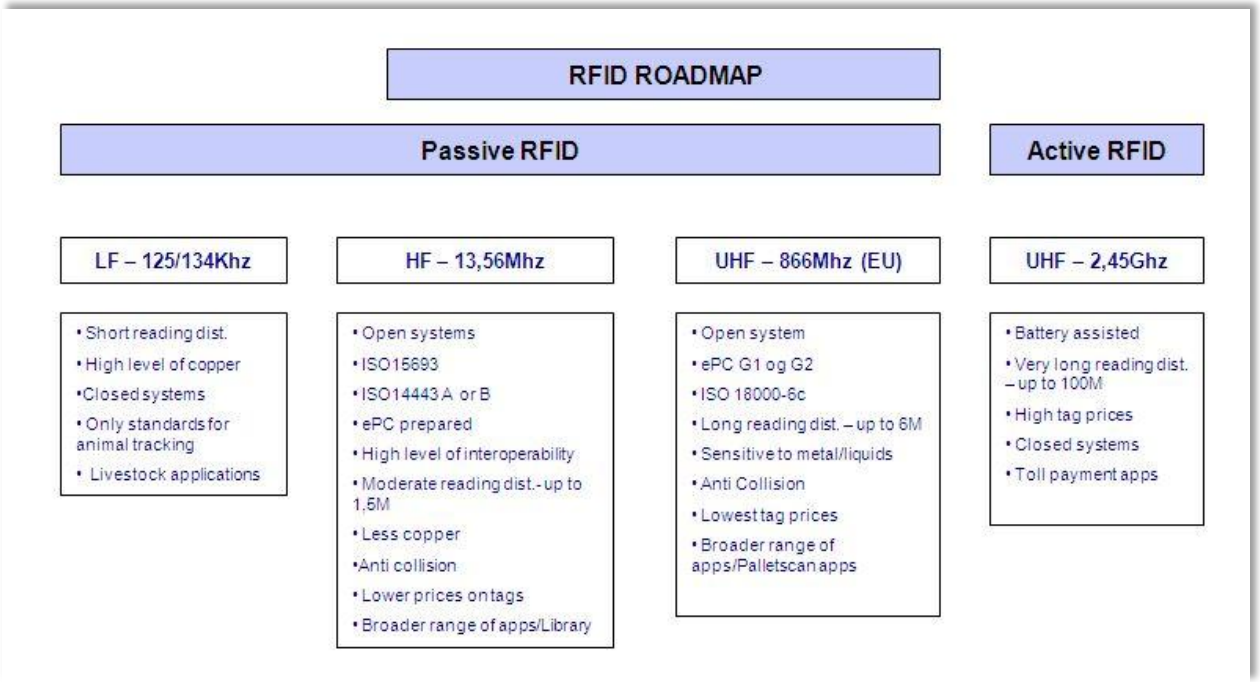


Figure 12 – RFID Overview

4.1.4.1. Low Frequency - 125…134 KHz

The 125 KHz frequency is very good with liquids and metal. However, this frequency often has a proprietary protocol, and the tag pricing is therefore quite high. It has a short reading distance and a high level of copper in the tag. It is a closed system with only standards existing for animal tracking. This is a passive technology. Other attributes include:

- Short reading distance
- High level of copper
- Closed systems
- Only standards for animal tracking
- Livestock applications

4.1.4.2. High Frequency - 13,56 MHz

The 13.56 MHz Freq is good with liquids, but is affected by the presence of metal. This frequency offers global harmonisation, and the tag pricing is coming down. The UHF frequency excels where range and

transmission speed is needed, and where a project can only be realized with low tag pricing. This is a passive technology. Other attributes include:

- Open system
- ISO15693
- ISO14443 A ogB
- ePC prepared
- High level of interoperability
- Moderate reading distance- up to 1.5M
- Less copper
- Anti collision
- Lower prices on tags
- Broader range of applications and libraries

4.1.4.3. Ultra High Frequency - 868 MHz (EU)

The UHF frequency excels where range and transmission speed is needed, and where a project can only be realized with low tag pricing. Other attributes include:

- Open system
- EPC Gen 2
- ISO 18000-6c
- Long reading dist. – up to 6M
- Sensitive to metal/liquids
- Anti Collision
- Lowest tag prices
- Broad range of applications like pallet scanning

4.1.4.4. Ultra High Frequency - 2.4…5.4 GHz

Designed for proprietary systems and highly focused and specific segments such as toll payment, container logs and sensor tags for monitoring pressure, humidity and/or temperature.

The difference from passive technology is the need of external energy such as a battery, but batteries with very long life time which again depends on the use of the tag. This means significantly higher prices, but performances are very long read ranges (up to 100M) with high amount of data as well as a log on the tag. This makes the tag expensive. It is a closed system.

- Battery assisted
- Very long reading distances. – up to 100M
- High tag prices
- Closed systems
- Toll payment apps

4.1.4.5. The EPC Gen 2 Standard

EPC Gen 2 is short-hand for the Electronic Product Code Class-1 Generation-2 UHF RFID Protocol, the specification developed by EPCglobal for the second generation RFID air interface protocol and one example of a passive RFID tag protocol. EPC Gen 2 was developed to establish a standard for RFID tags used in supply chain applications (e.g., tracking inventory). The current ratified standard for Class 1 devices operates in the ultrahigh frequency (UHF) range (860 – 960 MHz), supports operation at long distances (e.g., 25-30 feet), and has minimal support for security (e.g., static passwords to access or kill information on the RFID device).

4.1.5. Human Readable (OCR)

The EFPIA have recommended that human readable text is applied to the carton pack along with the GS1 Data Matrix code.

For human readable text there exist no standards like bar code grading. The regulations say that text must be legible to the human eye but no one has defined what this means. It is up the equipment suppliers to define how they will measure individual characters for correctness and up to the end user on how they will specify and qualify this measurement.

There are two factors to measure here:

- **Print Identity** – can the print always be identified as the correct information that was applied to the pack.
- **Print Quality** – does the print have an acceptable overall quality (irrespective of its legibility).

Most suppliers of machine vision approach the above two measurements as a common single measurement, that of the 'shape score' of the character, or how well it resembles a pre-trained model.

The choice of font (or style of character) is very important here. A font should be chosen that gives good physical differences between like characters, or good 'Optical Separation'. The font with the best available optical separation is the machine font OCRA. This style of print appears at the bottom of a cheque book. These magnetic ink numbers allow the cheque to be 'captured' by the bank where it is deposited or cashed.

The other machine reading font is OCRB. This font appears at the bottom of a UPC code. This code appears quite pleasant to the eye and has been the font of choice for a number of application.

A number of users have also stipulated the removal of 'like' characters from the alphanumeric font to be used for serialisation, such as I and 1 and 0 and O for example.

4.2. Marking and Printing Technologies

4.2.1. The Purpose of Marking

For Track & Trace applications, the selection of the marking technology is a fundamental step as the information to be printed may content important product information's.

Product identification

- Marking of alphanumeric text
- Marking of standardised codes – 2D Matrix Code/ GS1 Composite Code / Linear Barcode
- Graphics (e.g Logo, Symbol)

Track and Trace

- Identification with GTIN number, Lot/Batch number, Expiry Date, Serial number
- Compliance with regulations

Safety

- Anti-Counterfeiting measures
- End customer security with focus on patient compliance

Cross media marketing

- Connecting marketing mediums, channels and products through the use of QR codes

This selection of marking technology needs analysis of:

- The material (substrate) to be marked
- The speed of the object to be marked
- The frequency of the object to be marked
- The data volume (bar code included ?) to be marked

4.2.2. Continuous Inkjet (CIJ) Technology

How it Works

In continuous inkjet technology, a high-pressure pump directs liquid ink from a reservoir through a gun body and a microscopic nozzle, creating a continuous stream of ink droplets using the phenonomen known as Plateau-Rayleigh instability. A piezoelectric crystal creates an acoustic wave as it vibrates within the gun body and causes the stream of liquid to break into droplets at regular intervals – 64,000 to 165,000 droplets per second may be achieved .As the ink droplets form they are subjected to an electrostatic field created by a charging electrode. The applied field is varied according to the degree of drop deflection required. This results in a controlled, variable electrostatic charge on each droplet. Charged droplets are separated by one or more uncharged “guard droplets” to minimize electrostatic repulsion between neighbouring droplets.

Figure 13
Typical CIJ installation

Figure 14
CIJ marking sample

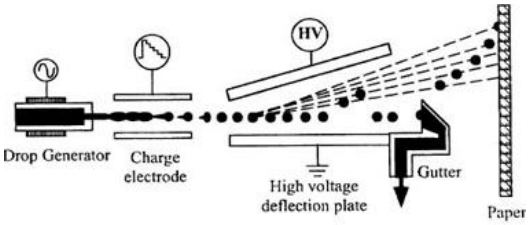


Figure 15
Functional diagram of CIJ technology

Most common CIJ applications

CIJ is the most widely used marking technology. Typical applications include:

- Marking of beverage cans and bottles
- Marking of cartons and boxes
- Marking of labels

Figure 16 – Typical CIJ Marking Samples

4.2.3. Thermal inkjet (TIJ) Technology

Thermal Inkjet is also known as Bubble Inkjet

Most home or office (consumer) inkjet printers use print cartridges. These print cartridges comprise a series of tiny chambers each containing a heater, all of which are constructed by photolithography. To eject a droplet from each chamber, a pulse of electrical current is passed through the heating element causing a rapid vaporisation of the ink in the chamber. This vapourisation forms a bubble, which causes a large pressure increase, propelling a droplet of ink onto the paper (tradename of Bubble Jet). The ink's surface tension, as well as the condensation and thus contraction of the vapour bubble, pulls a further charge of ink into the chamber through a narrow channel attached to an ink reservoir.

The inks used are usually water-based (aqueous) and use either pigments or dyes as the colorant. The inks used must have a volatile component to form the vapour bubble, otherwise droplet ejection cannot occur. As no special materials are required, the print head is generally cheaper to produce than in other inkjet technologies.

Figure 17
Typical TIJ installation

Figure 18
TIJ marking sample

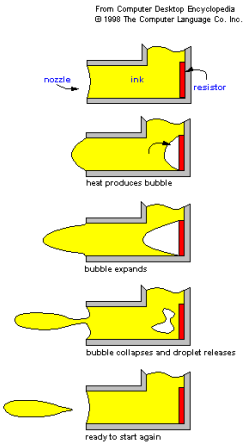


Figure 19
Functional diagram of TIJ technology

Most common TIJ marking applications

TIJ technology is most commonly used in home and office desktop printers. The technology has been adapted for coding and marking on cartons in the Pharmaceutical industry and other sectors where the printed material is absorbent.

Figure 20 – Typical TIJ Marking Samples

4.2.4. Thermal Transfer (TT) Technology

How it works

Thermal Transfer printers use the same basic technology as direct thermal printers, but replace chemically coated paper with a non-sensitized face stock and a special, inked ribbon. A durable, polyester ribbon film coated with dry thermal transfer ink is placed between the thermal printhead and label. The thermal printhead transfers the ink onto the label surface, where it cools and anchors to the media surface. The polyester ribbon is then peeled away, leaving behind a stable, passive image.

Figure 21
Typical TT installation

Figure 22
TT marking sample

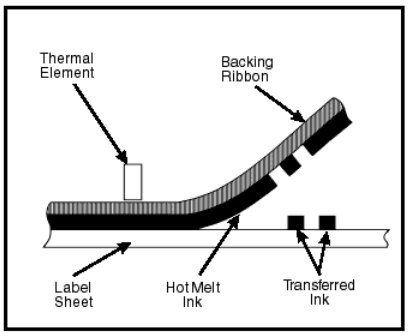


Figure 23
Functional diagram of TT technology

Most common TT marking applications

TT is most commonly used in print and apply applications. Common usages range from price ticket printers used in supermarkets to carton print and apply label printers.

Figure 24 – Typical TT Marking Samples

4.2.5. Laser Marking

How it works

Laser marking is a method for labeling various kinds of objects using a laser. The principle of laser marking is that a laser beam somehow modifies the optical appearance of a surface that it hits. This can occur through a variety of mechanisms:

- ablation of material (laser engraving); sometimes removing some colored surface layer
- melting a metal, thus modifying the surface structure
- slight burning (carbonization) e.g. of paper, cardboard, wood, or polymers
- transformation (e.g. bleaching) of pigments (industrial laser additives) in a plastic material
- expansion of a polymer, if e.g. some additive is evaporated
- generation of surface structures such as small bubbles

Figure 25
Typical laser marking apparatus

Figure 26
Laser marking sample

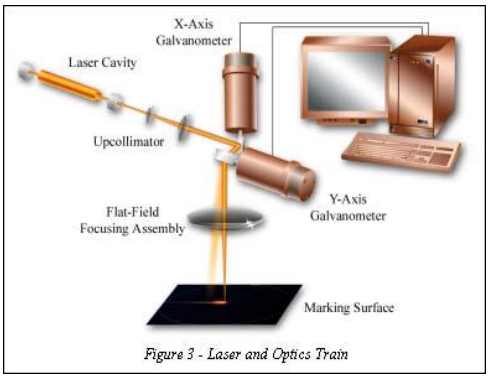


Figure 27
Functional diagram of laser technology

Most common laser applications

Laser marking is commonly used for direct product marking applications and is the second most used marking technology in pharmaceutical track and trace applications

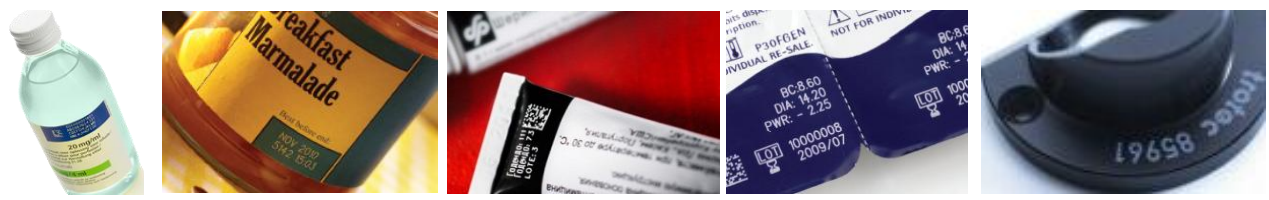


Figure 28 – Typical Laser marking samples

4.2.6. Drop on Demand Piezo inkjet (DOD Piezo)

How it works

Most commercial and industrial inkjet printers and some consumer printers use a piezoelectric material in an ink-filled chamber behind each nozzle instead of a heating element. When a voltage is applied, the piezoelectric material changes shape, which generates a pressure pulse in the fluid forcing a droplet of ink from the nozzle. Piezoelectric (also called Piezo) inkjet allows a wider variety of inks than thermal inkjet as there is no requirement for a volatile component, and no issue with kogation (buildup of ink residue), but the print heads are more expensive to manufacture due to the use of piezoelectric material (usually PZT, lead zirconium titanate). A drop-on-demand process uses software that directs the heads to apply between zero to eight droplets of ink per dot, only where needed.

Piezo inkjet technology is often used on production lines to mark products - for instance the "use-before" date is often applied to products with this technique; in this application the head is stationary and the product moves past. Requirements of this application are high speed, a long service life, a relatively large gap between the print head and the substrate, and low operating cost

Figure 29
Typical DOD piezo print & supply unit

Figure 30
Sample of the many direct product printing application

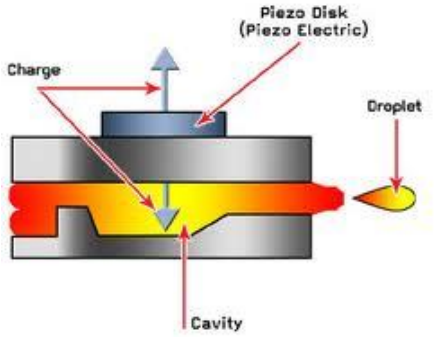


Figure 31
Functional diagram of drop on demand piezo technology

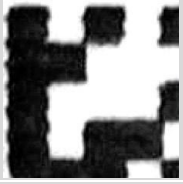
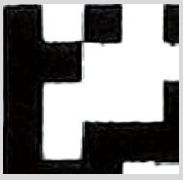
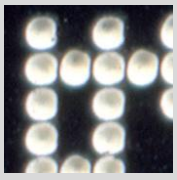
Most common DOD application

The DOD piezo technology is used a wide and expanding range of applications including:-

- Direct product printing and marking
- Label printing and marking
- Contactless printing
- Brand & product printing

Figure 32 – Typical DOD Piezo Samples

4.2.7. Comparison of the Marking Technologies

	Continuous Inkjet (CIJ)	Thermal Inkjet (TIJ)	Thermal Transfer (TT)	Laser Marking	DoD Piezo Inkjet (DOD)
Quality and performance					
Print Quality	Low	Moderate	High	Moderate	High
Typical Bar Code Grade	C/D-Grade	C/B-Grade	A-Grade	C/B-Grade	A-Grade
Print Performance	Printing performance is dependent on the line speed, data density and image resolution. See also Table 3 - Comparison of Marking Technologies for a comparison of how these factors effect each technology				
Native print width Narrow <12mm Medium >12mm, <50 mm Wide >50mm	Narrow	Medium	Wide	Narrow/ Medium	Narrow/ Medium
Printing distance from substrate to print head	Long distance	Close	Physical contact required	Long distance	Close
Scanner readability	Low	Low/Moderate	Excellent	Moderate	Excellent
Cost Considerations					
Investment costs	Low	Moderate	Moderate/High	High	High
Operating costs	Low	High	Moderate/High	Low	Low/Moderate
Environment impact	Low	High	High	Moderate	Low
Operational considerations					
Substrate pretreatment required?	Yes, if there is no absorbing area on substrate	Yes, if surface area is not suitable for ink absorption	Generally none	Yes, High contrast (dark) or pretreatment of laser area is a must	Generally none
Decap Time	Minutes to hours	Minutes to hours	None	None	Days for UV inks, less for other ink technologies
Ink technology	Solvent based	Water based	Ribbon	None – substrate abrasion	Solvent, Oil, Resin, Water based & UV cured inks
Code, texts and graphics					
Alphanumeric	Yes	Yes	Yes	Yes	Yes
Bar Code	Yes *	Yes *	Yes	Yes *	Yes
2D Codes	Yes *	Yes *	Yes	Yes *	Yes
GS1 Composite Code	No	No	Yes	Yes *	Yes
Graphics	No	Yes	Yes	Yes	Yes
Best practise	It is recommended that the complete coding, text and graphics requirements are tested and proven on original samples of the proposed substrate. These samples should then be proven with image grading and durability tests.				
How the technology reproduces the 2D matrix image Magnification of sample markings					
Print examples					

Note: * The ability to print bar codes and 2D bar codes with this technology may be limited to certain images sizes (i.e. not too small) in order to produce a readable and gradable image.

Table 3 - Comparison of Marking Technologies [11]

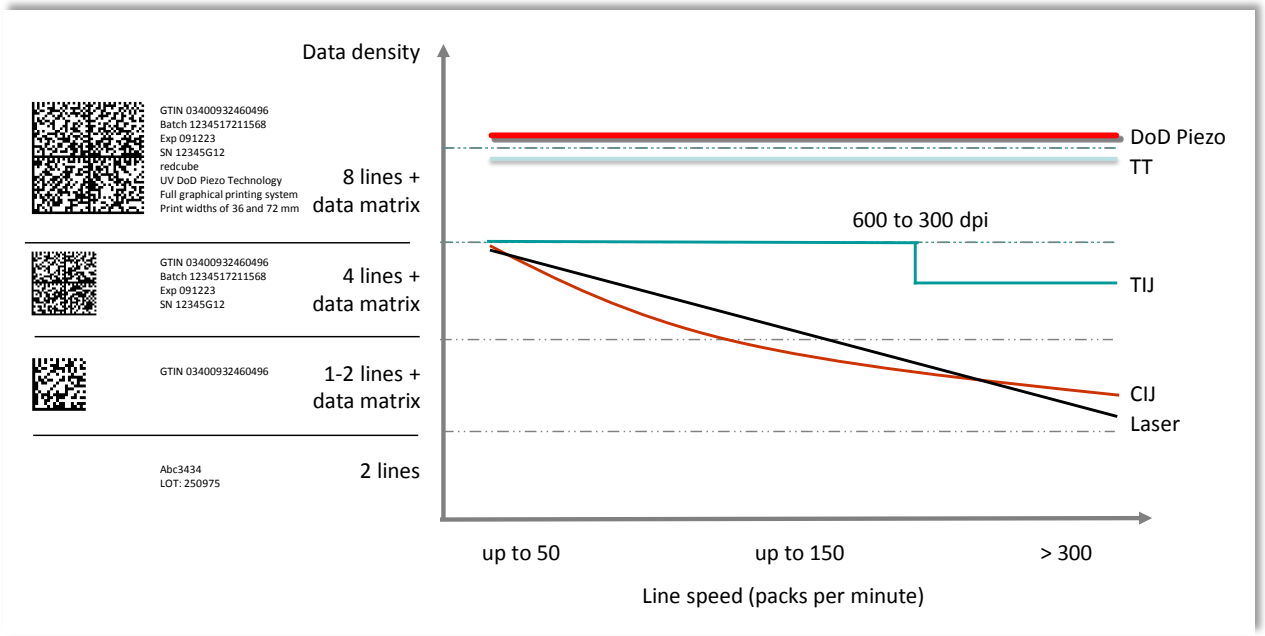


Figure 33 - Comparison of marking technology performance:

Data density & print resolution vs printing speed

[11] *Source Hapa AG, 2011*

	Advantages	Limitations
Continuous Inkjet (CIJ)		
	Low investment cost High line speed Wide range of printable substrates available	Mainly restricted to printing code with low image quality and low image perception Short decap time perceived as a „messy“ technology
Thermal Inkjet (TIJ)		
	Its easy and simple to use High speed printing 2D Codes & Barcodes Most prolific technology for pharmaceutical track and trace (carton marking)	High operating costs (frequent line stoppages, product wastage) Short de<cap time and lost pins are common problems High environmental impact - Used cartridges are consider “special waste”, and are difficult and costly to dispose of and recycle.
Thermal Transfer (TT)		
	High speed printing, not depending on dpi High native print width High barcode grade and excellent scanner readability	Requires physical contact with the substrate Ribbon waste leads to high environmental impact Operating and waste disposal costs are high
Laser marking		
	Printing all codes and graphics Low operating costs No decap time limitations	Often need to pretreat the printable area in order to provide a high contrast background to the laser marks High investment costs and integration costs due to need to include fume extraction systems Potential for production site/line pollution
DOD Piezo (DOD)		
	DOD Piezo enables consistent high end marking with the best image quality on a wider range of printable substrates Low running cost Flexibility and marking versatility	The space required for integration High investment cost

Table 4 - Key advantages and limitations of the marking technologies [12]

4.2.8. Criteria for Choosing a Marking Technology

There are numerous factors which will influence the optimum choice of marking technology. It is important to consider not only short term marking requirements, but also those of the medium/long term. Here are a number of factors that should be considered:-

- Which range of substrates need to be marked?
- Which pre-treatment processes make sense and are cost effective in your packaging supply chain?
- What printing speeds / widths/ resolutions (dpi) are required?
- What needs to be printed and marked and what impact does the marking quality have upon your end customer, brand and sales channels?
- What are your typical batch sizes, total print volumes? How does your print and marking technology choice effect your line productivity and efficiency: will line stoppages caused by your printing technology choice effect your operation?
- What is the printing frequency and is decap time a critical factor?
- How critical is print resistance /image durability? (Logistic, consumer safety)?

[12] *Source Hapa, AG 2011*

- How will the marking technology be integrated into packaging/production line? (Space requirements, track and trace, serialisation, integration with visioning systems, environment sensitivity and control etc.)
- Does your choice provide future flexibility to respond to changing marking needs?
- What is the correct balance between the initial investment and long term operating costs?
- What are the environment impacts and associated costs related to the technology choice?

Depending on this different technologies are suitable. The following matrix (provided by Domino, UK) shown in Table 5 gives a rough overview about influence of these factors for different marking technologies.

The requirements are split by;

- All substrates
- Two code formats
  Basic = 2 line and/or simple 2D
  Complex >2 line and/or complex 2D e.g. 26 x 26)
- Three Speeds
  L = <20 metres per min
  M = 20 - 50 metres per min
  H = >50 metres per min

Each are then graded by;

- Green (Achievable)
- Amber (Possible with caveats)
- Red (Not possible)

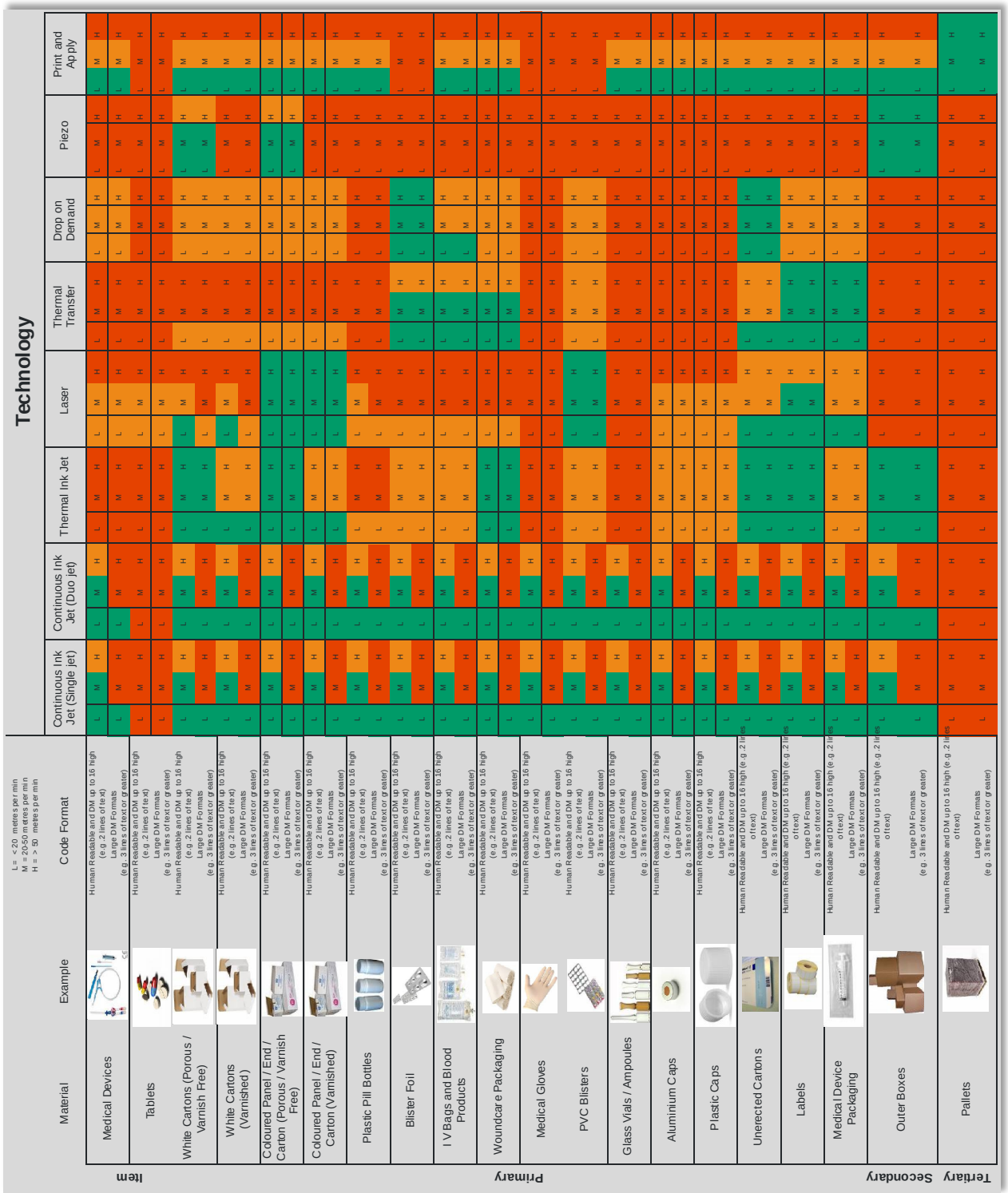


Table 5 – Marking Technology Matrix [13]

[13] *Source – Domino UK 2011*

4.2.9. Labelling

Unique pre-numbered labels applied to cartons or containers. Here print quality of 'Grade A' bar codes can be continuously guaranteed.

Labels and cartons may be printed locally off line or even be printed 'in line' complete with serialisation using the new generation of high quality printers, here again print quality of 'Grade A' bar codes can be continuously manufactured.

Figure 34 – High Quality Label

4.3. Marking & Print Quality Verification (Grading)

As with any critical printing and marking application, there is a need to verify the quality of what has been marked on the pack.

Global applications with multiple scanning systems require a bar code quality to guarantee scanning accuracy. Bar code verification is an important part when using bar code in a global supply chain. The verification must be done against the ANSI/CEN/ISO (American National Standards Institute/Committee for European Normalization/International Standards Organization) guidelines.

Reasons to verify a bar code:

- Improve quality. To ensure maximum reliability in the interface between bar code printing and scanning technologies.
- Increase productivity. To achieve high first-time read rates. Good bar code quality will guarantee that every scanning system can read the bar code.
- Avoid unnecessary complications. To avoid compliance penalties and production line shutdowns. Poor bar code quality may result in data substitution errors, which is critical especially in security applications. E.g. does the German securPharm initiative definitively specifies not to print the serial number in a human readable string. Concern, that a high rate of false inputs would result in case the serial number is entered manually to a system. Therefore the machine readable number (inside bar code) must be 100% checked for readability.

Verification methods are:

- Traditional (today not used anymore)
  Checks for encodation, print contrast signal (PCS), average bar deviation, wide-to narrow ratio, checksum (optional) and will result in a passed or failed.
- ANSI/CEN/ISO minimum, quiet zones, symbol contrast, modulation, defects, decodability and will result in a grade A (perfect) to F (failed).

Note!

Bar code reading and content matching is not verification! Checks for global threshold determination, reflectance minimum, edge contrast

Scanners can not be used for bar code verification due to the difference in design of scanners and verifiers. A scanner cannot determine the absolute quality of a printed bar code. A bar bode scanner is a data collection tool, ideally it should do this easily and quickly even on poorer quality of the bar codes. The ability of a scanner to read the bar code is based on its (individual) decoding capability. Thus, a bar code of poor quality may be decoded correctly by one scanner, but not by another. A verifier is a precision instrument designed to provide constant and repeatable measurements of a symbol. A verifier should perform in strict accordance with global accepted ISO standards. A verifier has to be calibrated before use.

For pharmaceutical marking applications, this verification or inspection of the printing quality usually falls into two separate functions:

4.3.1. OCR Print Quality

It is much more difficult to specify quality criteria for OCR readers, as no general standards are in place, individual criteria listed in a project URS may be used.

4.3.2. Bar Code Quality

For bar codes there is a related specification, for example the current international bar code quality specification is ISO/IEC 15416 for linear bar codes and ISO/IEC 15415 for 2D bar codes. The bar code quality specifications seek to measure or more correctly 'grade' the bar code in terms on its printed or marked quality using different parameters. Each test is given a grade from 0 (worst) to 4 (best) and the lowest of any of the tests is the scan grade given to the bar code. For most common applications a 1.5 grade is the minimum acceptable grade that should be produced.

Bar Code Quality Grade	ISO (numerical)	ANSI (alphanumerical)
Very good	3.5 to 4.0	A
Good	2.5 to 3.5	B
Satisfactory	1.5 to 2.5	C
Sufficient	0.5 to 1.5	D
Faulty / not suitable	< 0.5	F

Table 6 - Relation of ISO (numerical) to ANSI (alphanumerical) Quality Grades.

On-Line Quality Inspection

Some camera systems offer within the bar code reading the possibility to verify the bar code quality (grade) with ISO/ANSI parameters, which allows performing a 100% inspection in the production cycle.

Questions concerning the resulting quality grades in comparison to fully conform verifiers are arising very often. Differing results between calibrated verifiers and results evaluated from an on-line camera system are mainly caused by different conditions during image acquisition. These are especially non optimised lightings (available space) and non constant reading conditions (speed, distance and angle).

Typical features of an inline verifier are:

- The image acquisition is performed on the machine in process and a 100% inspection is performed.
- The bar code may be in movement during the inspection.
- The available evaluation time is strictly limited.
- Bar code not matching the minimum required quality grade is ejected or a warning output is activated.
- The measuring result is less accurate as with a calibrated offline system due to variations during the measuring process. This can be caused by the different lighting and optical set-up, not equal to the required conditions within the international standards.
- The verification results may not be 100% comparable with other verifier results. Especially if different measuring conditions and calibrations are used. The required measuring conditions specified in the ISO/IEC standards may not be convertible to the machine conditions.
- Bar Code not matching the minimum required quality grade are ejected or a warning output is activated.

Camera systems are designed for a fast on-line reading; typical features of calibrated off-line verifiers therefore may not exist (i.e. measuring protocol). Therefore it is recommend referencing the on-line verification results with a calibrated system, reproducible results can be achieved with a procedure documented.

Possible influence to on-line bar code verification

Influence	1D-Barcode	GS1 Data Bar	Data Matrix	Composite Code
Reading angle	Code distortion possible, 90° recommended	Code distortion possible, 90° recommended	Code distortion possible, 90° recommended	Code distortion possible, 90° recommended
Reading distance	if resolution changes	if resolution changes	if resolution changes	if resolution changes
Reading during movement	Camera shutter time	Camera shutter time	Camera shutter time	Camera shutter time
Lens type ❶	Minor	Minor	Minor	Minor
Lens aperture ❶	Minor	Minor	Minor	Minor
Focal set up	yes	yes	yes	yes
Camera gain ❷	yes	yes	yes	yes
Shutter time ❸	yes/no	yes/no	yes/no	yes/no
Lighting type	yes, if lighting is not homogenous	yes, if lighting is not homogenous	typically no, as the code is very small	yes, if lighting is not homogenous
Lighting colour	light colour influences contrast	light colour influences contrast	light colour influences contrast	light colour influences contrast
Camera resolution	low if ≥ 5 Pixel / X-Module	low if ≥ 7.5 Pixel / X-Module	low if ≥ 7.5 Pixel / X-Module	Low if ≥ 10 Pixel / X-Module
Measuring aperture ❹	High	High	High	High

❶ A suitable high quality lens adapted to the camera resolution is assumed. This lens shall be suitable to provide a good image quality with low influence of aperture set-up

❷ Depending from the camera image quality an increased signal gain will cause a poor image quality (noise) which results in non reliable verification results. The recommended maximum setting is to be documented with the application

❸ No influence if the image is captured during standstill. With moving objects the shutter time has to set to short values to avoid image smear. The recommended setting has to be documented in the application

❹ The measuring aperture is recommended to be set accordingly to the reading equipment resolution, the ISO 15415 recommends to operate a 0.8 X aperture. (X-Module = dot size)

Table 7 – Accuracy of on-line grading

International standards for bar code print quality verification.

- ISO/IEC - Symbology specifications if related, i.e. (ISO/IEC 16022 Symbology Specification Data Matrix)
- ISO IEC 15426 - Bar code verifier conformance specification - Part 1: Linear symbols
- ISO IEC 15426 - Bar code verifier conformance specification - Part 2: Two-dimensional symbols
- ISO/IEC 15415 - Bar Code Print Quality test Specification - Two-dimensional symbols
- ISO/IEC 15416 - Bar Code Print Quality test Specification - Linear symbols
- AIM DPM - Data Matrix direct part mark quality guideline

Reference Code

To validate the verification result of the used systems, calibrated conformance test cards are available.

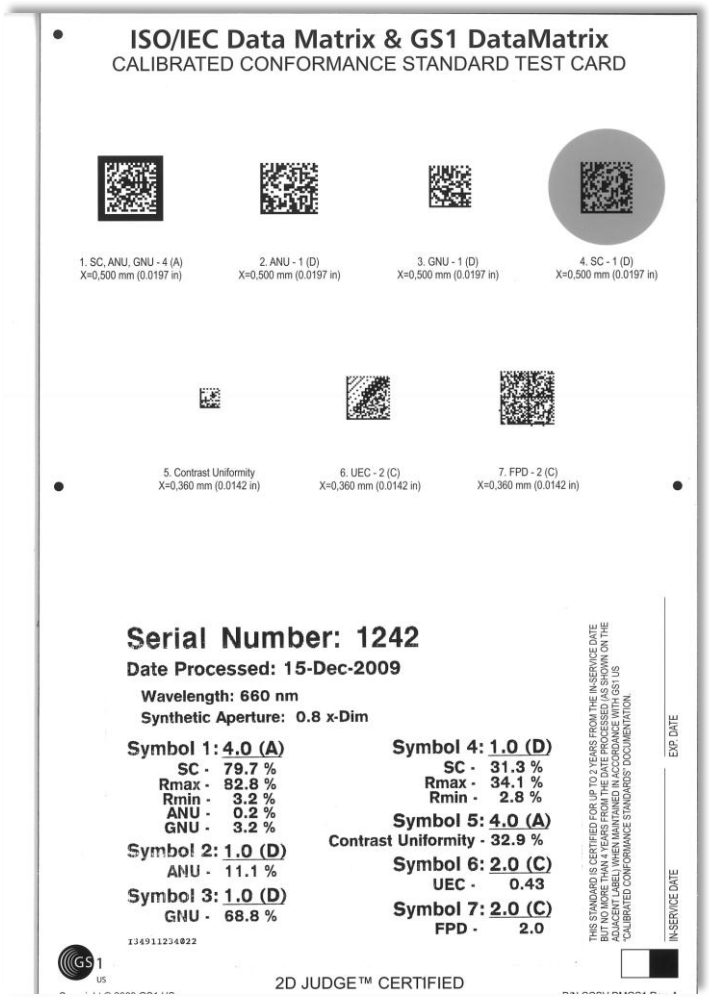


Figure 35 - GS1 Calibrated Conformance Test Card

4.3.3. Industry Related Bar Code Grading

To enable applicable and comparable results of various verifiers and for analysis of the intended application following parameters must be specified, especially if differing from the general ISO recommandations:

- Which symbology must be verified?
- The dimensional size (X-Module) of the bar code to be checked?
- The required resolution (reference to the reading device)?
- Which measuring aperture must be selected?
- Which lighting or scanning technology (laser scanner) is used in the intended application?

Within the industry related specifications, the user can find such specific requirements. E.g.:

- For France the CIP specifies to use ISO 15415 - 1.5 06 / 670, which requires to use a fixed aperture of 6 mil (152 µm), red light with wavelength of 670 nm and the required minimum quality is grade 1.5 (C)
- In Turkey the required minimum quality is 0.5 (D)
- For GS1 code the X-Module size is specified on case the Code128 symbology is used and must be beween 0,25 (10 mil) and 1,016 (40 mil). The relating measuring aperture for 1D and 2D code shale 80% of the X-Module.

- The German PPN specification requires a minimum quality grade of 0.5 (D) and specifies red light (660 nm) for the light colour and again 80% of the code X-Module. The X-Module range is specified between 0,25 ,mm (10 mil) and 0.615 mm (24 mil). Dot codes are not

4.4. Data Structures used for Pack Marking

Standardised (e.g. ISO/IEC) data structures ensure the interoperability of data independent of the used data carrier, like bar code or RFID tags, and the used internal data structures.

Within pharmaceutical and health care industry there are two main standards which are used to ensure a worldwide, unique and clear data exchange.

GS1

See also 6.5 for more information about the GS1 organisation.

The GS1 standard is based on a unique symbol identifier, so called FNC1. The interpretation of any bar code contents is specified in case the reserved FNC1 symboly is used (typically in first position). The data following are structured by application identifier (AI) with specify the meaning and length of the data used.

For pharmaceutical use several application guidelines are provided by the GS1.

Within track & trace application following AI (application identifier) typically will be used:

- **(00)** - The Application Identifier (00) indicates that the GS1 Application Identifier data field contains an SSCC (Serial Shipping Container Code). The SSCC is used to identify logistic units
- **(01)** - The Application Identifier (01) indicates that the GS1 Application Identifier data field contains a GTIN. The GTIN is used to identify trade items
- **(10)** - The Application Identifier (10) indicates that the GS1 Application Identifier data field contains a batch or lot number. The batch or lot number associates an item with information the manufacturer considers relevant for traceability of the trade item to which the Element String is applied. The data may refer to the trade item itself or to items contained. The number may be, for example, a production lot number, a shift number, a machine number, a time, or an internal production code.
- **(15)** - The Application Identifier (15) indicates that the GS1 Application Identifier data fields contain a best before date. The best before date indicates the ideal consumption or best effective use date of a product. It is a statement about quality. It is often referred to as a sell by date or a minimum durability date.
- **(17)** - The Application Identifier (17) indicates that the GS1 Application Identifier data fields contain an expiration date. The expiration date is the date that determines the limit of consumption or use of a product. Its meaning is determined based on the trade item context (e.g., for food, the date will indicate the possibility of a direct health risk resulting from use of the product after the date, for pharmaceutical products, it will indicate the possibility of an indirect health risk resulting from the ineffectiveness of the product after the date). It is often referred to as "use by date" or "maximum durability date."
- **(21)** - The Application Identifier (21) indicates that the GS1 Application Identifier data field contains a serial number. A serial number is assigned to an entity for its lifetime. When combined with a GTIN, a serial number uniquely identifies an individual item.

Further AI are available inside the GS1 system, in total more than 100.

Example of a typical GS1 code data string (based Data Matrix), including the GTIN, expire date, batch number and a serial number:

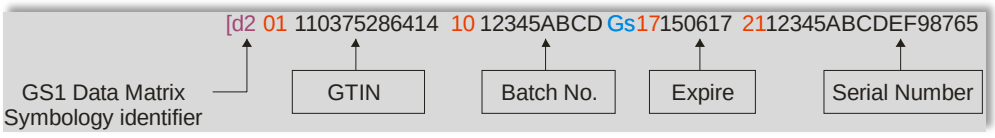


Figure 36 - GS1 Data String

FNC1 with Data Matrix ➔]d2 (symbology identifier for Data Matrix with FNC1)
FNC1 Separator ➔ <GS> as a group separator

ISO / ANSI

Beside the GS1 structure, ISO/IEC standards are in place as well, to embed such structured data into a bar code. Compared to GS1 the ISO/IEC standards are more open and can handle different data structure models (e.g. GS1, HIBC or PPN) with more open standards.

One initial requirement for using these standards and to guarantee the uniqueness of the numbers is to follow ISO/IEC 15459-3:2006: This standard specifies the common rules that apply for unique identifiers for item management that are required to ensure full compatibility across classes of unique identifiers.

The standard ISO/IEC 15418 references to GS1 General Specification and ANSI MH10.8.2 for use of Application (AI - GS1) or Data (DI - ANSI MH10.8.2) Identifier, which are required to build a structured data content. The ISO/IEC 15434 standard specifies a transfer structure, syntax, and coding of messages and data formats when using high-capacity ADC media.

For the planned PPN code (Germany) the ISO/IEC based data structure uses 3 steps to geberate a worldwide unique data string:

1. A special control character(Macro 06) inside the Data Maatrix, causes the bar code scanner to interpret the following data conform to ISO/IEC 15434 (header / terminator) message format.
2. A reserved DI (data identifier) 9N (reserved for IFA GmbH) identifies the new PPN data structure following
3. A product registration agency code 11 identifies the PZN number inside the PPN number

E.g. in order to use the system for other countries, it is just required to reserve an additional registration agency code.

Within the ANSI MH10.8.2 DI are reserved for GS1 and HIBC, which guarantees that e.g. a PPN number is worldwide unique.

Example of a typical ISO/IEC based data string, including the PPN, expire date, batch number and a serial number:

Figure 37 - PPN Data String

5. The Pharmaceutical Pack Marking Situation Today

5.1. Argentina


The Ministry of Health Argentina schedules to go with serialization for pharmaceutical products.

Item level (carton)

GS1 Data Matrix is requested. GS1-128 or RFID are considered as well at the start phase. The code must contain GTIN (Global Trade Item Number) and Serial Number. To print expiry date or batch number is optional. The use of GLN (Global Location Number) is also recommended.

- GS1 as a Datamatrix code is selected for item level. GS1-128 and RFID are also considered in the start phase or if the lab has already started implementing RFID.
- The GS1 must contain GTIN and serial code.
- The inclusion of Batch & Expiry in the GS1 code is optional but it is a must that they are stored in the database of the batch with the serial number list.
- The use of the GLN (global trade location number) is also recommended.
- For shipping boxes and pallets RFID is suggested as best option (but the use of GS1 Datamatrix is not forbidden).

Shipping box and pallets

RFID is suggested as best option. Use of GS1 Data Matrix is optional.

Timeline:

Start with first phase at item level 01. January 2012.

Start with second phase (complete solution) scheduled for 01.07.2012

Summary

Step	Actual Status
Specification Source	Resolution 435/2011
Method of Serialisation	GS1 Data Matrix, GS1-128, EPC/RFID GTIN and serial number must be contained
Level of Serialisation	Item level (carton box)
Anti Counterfeit Features	Security labels, which cannot be removed free of residues, are required. Labels shall include a visual code
Deadline	Set up until 15.12.2011 Validation 6 month later

5.2. Brazil


On January 14 2009, in an effort to curb the growing counterfeit market, Brazil passed a law (**Nº 11.903)** mandating the drug manufacturers and distributors to act on the specific serialization and track and trace requirements of electronic identification and data capture. This three year plan has a very aggressive deadline laid out by the Brazilian government.

Brazil's current traceability proposal as laid out by the national regulatory agency ANVISA is to include a serialised code in 2D Data Matrix format - replacing the current linear bar codes - and a security hologram printed by the national mint which would be co-located with the Data Matrix code on a self-adhesive label.

The hologram would replace the 'raspadinha' label, which is based on coin-reactive ink and has been widely used on Brazilian pharmaceuticals for a number of years.

A shift towards Turkey's system would signal a dropping of the requirement for government-supplied security label, which according to the current proposals would have to be applied to the product within

Brazil. The pressure for this comes from the pharmaceutical manufacturers in order to avoid the additional cost of the hologram bearing serialised label.

Summary

Step	Actual Status
Specification Source	Anvisa
Method of Serialisation	GS1 Data Matrix pre-printed labels (expected to be changed)
Level of Serialisation	Item level (carton box)
Anti Counterfeit Features	Tamper evident label, aut-adhesive labels
Deadline	January 2012, probably postponed

5.3. China

On April 9, 2008 China's State Food and Drug Administration (SFDA) made it mandatory for serialisation to occur on each individual saleable pharmaceutical product units. This will be required for 275 therapeutic drug classes by December 2011.

The regulation mandates all drugs sold in the Chinese marketplace not just those manufactured in China. This can be used in conjunction with the China National Medicine Code (similar to GTIN).

Primary reasons for this Track and Trace initiative by China is to combat drug counterfeiting, improve patient safety, track the drug movements through the supply chain, support trace and recall, support a nationwide early warning system to alert authorities in case of abnormal drug movements as well as to make online, phone and SMS authentication available to field inspectors and end users.

China has decided on a 20 digit numeric number for their serialization effort. The 20 digits include a 6 digit manufacturing code which is the same as China's GTIN, a 9 digit serial number (provided by SFDA) followed by a 4 digits for checking and encryption. The data carrier format is 128C linear bar code. Both case and pallet serialization is also required.

Key Points:

- Linear bar code, not 2D code
- Direct or pre-printed labels
- Certified interface to the governmental database
- Difficult for foreign suppliers as Chinese government not divulging what is required for certification

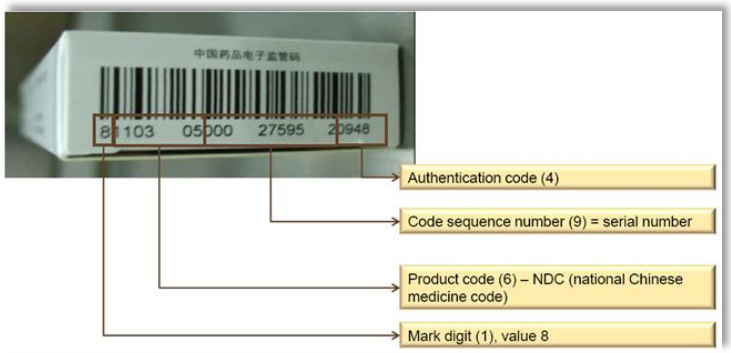


Figure 38 - Carton Box Coding for China

Summary

Step	Actual Status
Specification Source	t.b.d
Method of Serialisation	Pre-printed labels, GS1-128 code, check serial number against government database
Level of Serialisation	Item level (carton box)
Anti Counterfeit features	not yet specified
Deadline	Not yet known

5.4. European Union

 The UE directive (see 5.4.1) provides the principal rules and timeframe to implement a tool to prevent form counterfeit products. The technical conversion is related to the individual national legislation.

5.4.1. The EU Directive

On July 1st of 2011 the directive 2011/62/EU of the European parliament and of the council, amending directive 2001/83/EC was published and is now in place. The timeline (see Figure 40) for the EU members started.

L 174/74 EN Official Journal of the European Union 1.7.2011

DIRECTIVE 2011/62/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 8 June 2011

amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114, and point (c) of Article 168(4), thereof,

Having regard to the proposal from the European Commission,

Having regard to the opinion of the European Economic and Social Committee(6),

medicinal products from other illegal medicinal products, as well as from products infringing intellectual property rights. Furthermore, medicinal products with unintentional quality defects resulting from manufacturing or distribution errors should not be confused with falsified medicinal products. To ensure uniform application of this Directive, the terms 'active substance' and 'excipient' should also be defined.

(6) Persons procuring, holding, storing, supplying or exporting medicinal products are only entitled to

Figure 39 – EU Directive Headline

All European member states will have to implement local legislation within 18 months. Given the legislators short timeframe it is important that manufacturers begin to evaluate and implement a solution as soon as possible, to include a requirement for features that enable the identification, authentication and traceability of prescription medicines.

After publication of the national conversion (delegate acts) a period of 3 years is available to introduce the national law. Some countries nay combine this with conversion of the directive 201/84/EU as regards pharmaconvigilance.

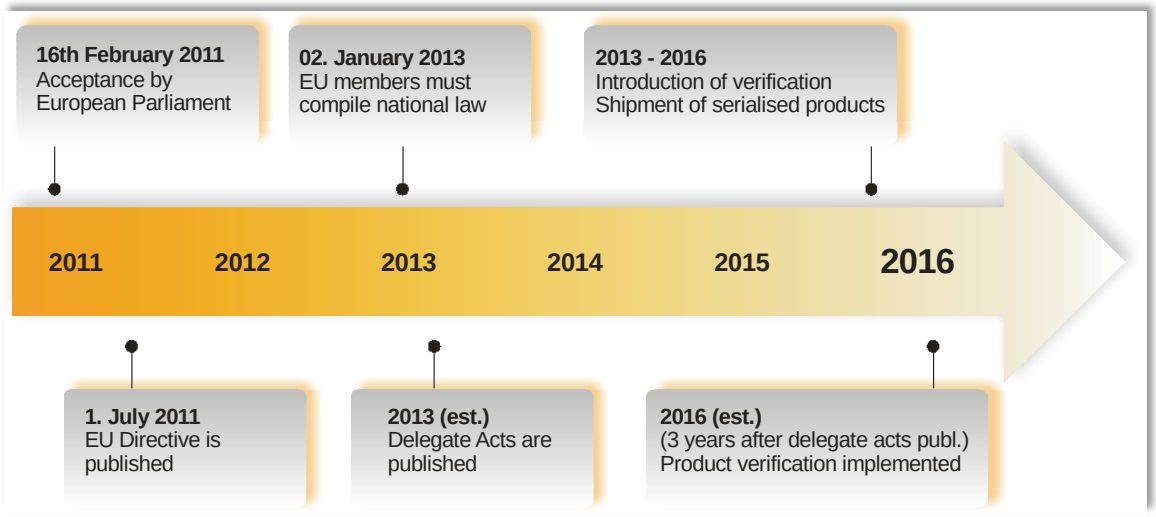


Figure 40 – EU Timeline

Two safety features should allow the verification of each supplied pack of the medicinal products, regardless of how they are supplied including through sale at a distance.

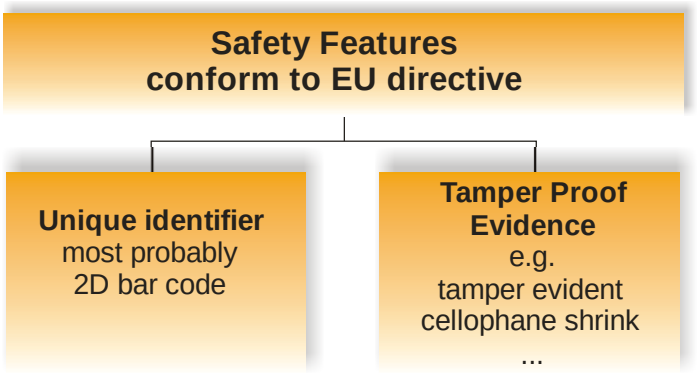


Figure 41 – EU Safety Features

- Serialization on carton level. Coding with unique serial number and bar code (e.g. GS1 Data Matrix). Product traceability through the supply chain (end-to-end solution)
- Temper evident packaging. Via label or packaging technologies

The field of applications of the safety features depends on the pharma product type.

- Rx (prescription only) drugs must contain the features as long they are not listed to be without risk of counterfeit. **White list (opt out)**
- OTC (over the counter) drugs must not contain the safety features as long they are not listed to be at counterfeit risk. **Black list (opt in)**

Criteria for counterfeit risk products are:

- Price and sales volume of drugs
- Number of detected counterfeit dugs in the past
- Specific features of drugs
- Severity of the treated sickness
- Other risks for the public health

The delegate acts have to care about:

- Specs of the unique identifier
- White list / Black list
- Procedure for announcement to the national authority
- Modality how to check the safety features
- Organisation of the database and interfaces

The parallel trader has to be compliant to the EU directive as well and has to replace the safety features in an equivalent way. The replacement is conducted in accordance to GMP Manufacturing authorisation holders including parallel traders shall be regarded as producers and therefore held liable for damages.

Still open questions are:

- Distinction OTC - Rx products (black list / white list)?
- EU-Database / national databases?
- Technical role-out?
- Scope of features?

5.4.2. Belgium

Belgium mandates that each reimbursable pack includes a sequential code, constructed from four different elements including a product identification number that is significantly different in form from the Italian 'Bollino'.

In December 2003, Belgium published a Royal Decree introducing sequential codes for all medicines to uniquely identify each product pack. Starting July 1, 2004 all packages had to carry a bar code containing a 16-digit sequential code structured as APB product identification number (7 characters), Sequential number (8 characters), and one character Check Digit (allocated by the manufacturer). The Decree did not mandate batch number or expiry date on the code. This is already used in nearly 60% of all pharmacies in the country.

It is the responsibility of the pharmaceutical manufacturers in Belgium to put these sequential codes on each pack as well as communicate them to the Evaluation and Medical Control Service of the INAM (public agency that runs the compulsory health insurance in Belgium) which runs the series of numbers for the Belgium market. Furthermore, it is at the manufacturer's discretion to print the sequential code directly on the external pack or to print it on a label that is put afterwards on the external pack (if using a label, it must be a non removable label).

Also, the Belgian Association of Pharmacists (APB) provides for each pharmaceutical product sold in Belgium Pharmacies a product identification number. Although using the number is optional it is widely used in Belgium's pharmaceutical industry as well as the distribution supply chain. This number consists of 7 characters and the only instance where the use of this number is mandatory is the reimbursable public packs as it is integrated into the sequential code (the first 7 characters corresponding to the APB product identification number). Linear / Stacked Bar code is required by law in Belgium.

No further details regarding the EU directive are currently known.

5.4.3. France

The overall timeline for the French CIP 13 coding requirements started in 2007 was as follows:

Q1 2007 - French Health Products Safety Agency (AFSSAPS) extended CIP code to 13 digits (from the original 7 digits) for all the existing products and published detailed correspondence information between the two types of codes. For the remainder of 2007 and as well as in 2008, all new products were allocated with both the 7 digit and the 13 digit code and the records were updated.

January 2008 – First batches of CIP 13 codes were released in the new 13 digit CIP code (syntax EAN 128) with the use of the 2D data matrix bar code (with expiry date and lot) on the external packaging.

January 1, 2009 - Only newly released products were to receive CIP 13 codes.

December 31, 2010 - All the new presentations of drugs will be released with the new CIP 13 codes as well as 2D Data Matrix bar code (with expiry date and lot) on the external packaging. Also by December 31, 2010, all pharmaceutical industry products distributed in France should have:

ECC200 Data Matrix bar code made up of Code CIP13, batch number, expiration date and human readable text.

- Pre-printed vignette sticker (used for reimbursements) consisting of CIP 13, the reimbursement rate and the price as well as the bar code.

More details about the data content are available from the document listed in ??. For availability of this and others, please refer to 6.2.

Figure 42 – CIP/ACL Specification Source

No further details regarding the EU directive are currently known.

5.4.4. Greece

Greece requires both a National Registration Number as well as a sequential number. Current plans expect a bollini solution with serialised a 1D bar code.

No further details regarding the EU directive are currently known.

5.4.5. Germany

A track-and-trace pilot for medicines has been announced in Germany in order to implement the new safety features for medicinal products required by the EU Directive 2011/62/EU for the German market. The securPharm (see 6.8) organisation was founded to involve the drug industry, wholesalers and pharmacists to improve the security of the pharmaceutical supply chain.

The pilot is expected to start on January 2013 and will specify to print an unique, serialised 2D Data Matrix code on unit of sales drugs (carton box), in order to allow them to be scanned and authenticated by pharmacists at the point of dispensing, following the EFPIA end-to-end verification system.

As a main difference to the EFPIA pilot run in Sweden, Germany plans to introduce two separate databases: In past the EFPIA's decision to operate a single database was one of the reasons why the EFPIA pilot was swapped from Germany to Sweden. The securPharm pilot will make use of two separate databases, one accessible to the pharmaceutical manufacturers and the other to the pharmacists. Wholesalers will be able to have access to the databases, in case a counterfeit product is suspected.

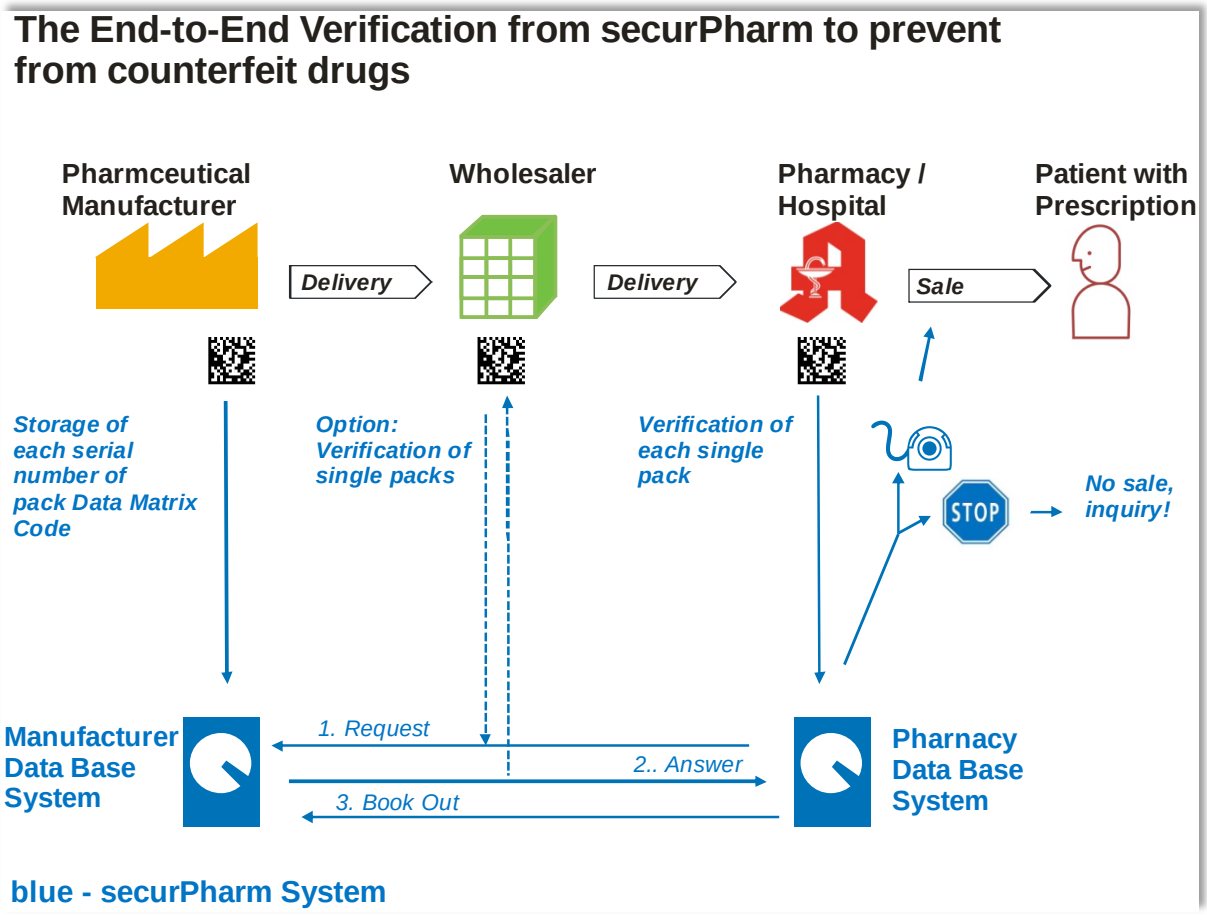


Figure 43 – securPharm Structure [14]

The securPharm Pilot should start with begin of 2013. The specification for the Data Matrix (ECC 200) code is available in German since 18.11.2001 (see 6.8.).

The 2D Matrix code won't be created by an existing issuing agency (like GS1) but by the IFA (see 6.7). The generation of a data string for the 2D Matrix Code will be based on following components:

- Pharmacy-Product-Number – PPN (made up of the current PZN to guarantee an unique international standardised number)
- Batch number
- Expiration date
- Serial number (unreadable as plaintext)

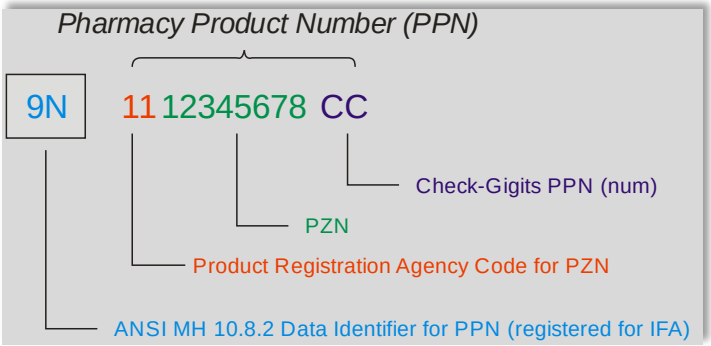


Figure 44 - Generation of PPN from PZN

[14] *Source - www.securpharm.com*

Figure 45 - Sample of securPharm carton box[15]

The Pharmacy-Product-Number and its specification does not include any aggregation or logistical guidelines. Anyway, the PPN is suitable to be used inside ISO/IEC 15394 (Bar code and two-dimensional symbols for shipping, transport and receiving labels) based transport logistics.

It is possible that other European countries will use the IFA principal (see Data Structures used for Pack Marking as well.

Applications for PPN-Code:

	PZN-Code ❶ Symbology PZN (Code 39)	**PPN-Code** Symbology: Data Matrix				
	PZN	PPN	Serial number	Batch	Exp. Date	GTIN
RX products	●	●	●	●	●	optional ❷
OTC products	●	●	optional	optional	optional	optional ❷
Other products	●	●	optional	optional	optional	optional

● Use mandatory

❶ Remains currently- PZN reservation (??) expires in 2016

❷ Optional for internal use

Summary

Step	**Actual Status**
Specification Source	EU directive, securPharm, IFA
Method of Serialisation	Direct marking, Data Matrix PPN data structure. Data Matrix with PPN number (PZN), serial number, batch & expiry date
Level of Serialisation	Item level (carton box) expected
Anti Counterfeit features	Required, not specified in detail
Deadline	National law – end of 2012 Pilot phase – 2013 Setup phase – end of 2015 Active from 2016

5.4.6. Ireland

Currently Irish serialisation requirements focus on haemophilia products.

No further details regarding the EU directive are currently known.

[15] *Source; IFA - www.ifaffm.de*

5.4.7. Italy

In Italy a system is in place that requires a sales pack must contain a unique 'Bollino', two bar codes: a product license number (AIC code) and a separate sequential number (human readable and 2/5 interleaved bar code) to combat reimbursement fraud.

The bollini must be purchased from the Italian ministry.

Figure 46 – Italian Bollino

Companies supplying into the Turkish market are investing in serialisation lines. No further details regarding the EU directive are currently known.

5.4.8. Portugal

No further details regarding the EU directive are currently known.

5.4.9. Spain

Spain is currently undertaking a serialisation initiative and is looking at the introduction of serialisation, this is being piloted. Companies supplying into the Turkish market are investing in serialisation lines.

?? Table ??

Summary

Step	Actual Status
Specification Source	EU directive
Method of Serialisation	ePedigree in discussion, GS1 2D code or RFID/EPC
Level of Serialisation	Unit/package level
Anti Counterfeit features	Not yet specified
Deadline	National law – end of 2012 Pilot phase – 2013 Setup phase – end of 2015 Active from 2016

No further details regarding the EU directive are currently known.

5.5. India

The Pharmexcil, (Pharmaceutical Export Promotion Council) has suggested three technologies-barcoding, digital mass serialisation with unique number and hologram technologies. Industry will have one year to implement the bar coding system if the proposal is officially adopted by the government

The MoHFW (Ministry of Health & Family Welfare, Government of India) has published a document to specify Track & Trace topics:

Phase 1: 01. October 2011

GS1 structured bar coding on primary level (blister) with GTIN. GS1 structured bar coding on secondary level (carton) with GTIN, expiry date and batch number. GS1 structured bar coding on tertiary level (shipping box) with GTIN, expiry date, batch number and SSCC (serial shipping container code)

Phase 2: 01. January 2012

Unique serial number on secondary (carton box) packaging level

Phase 3: 01. July 2012

Additional to phase 1 unique serial number on primary (blister) packaging level is requested.

Summary

Step	Actual Status
Specification Source	Ministry of Health & Family Welfare, Government of India
Method of Serialisation	GS1 Data Matrix, GS1-128, RFID, Aggregation of case level, GS1 SSCC
Level of Serialisation	Primary level - Blister GS1 2D bar code Secondary level - carton box GS1 1D / 2D bar code Tertiary level - Shipping case Gs1 bar code SSCC
Anti Counterfeit features	not yet specified
Deadline	1. October 2011 - Tertiary package level (shipping case) 1. January 2011 - Secondary package level (carton box 1. July 2012 - Primary package level (blister)

5.6. South Korea

The law for regulation of the pharmaceutical packaging market was published on May 30. Of 2011, but is still in a revision status. The marking requires a serial number, in the first step only selected drugs must be marked only. Later on all drugs must contain the batch related information, it is recommended to print the data in a human readable format as well. In case of less space available the serial number is not required to be printed as plain text. An aggregation might be required in later steps.

Summary

Step	Actual Status
Specification Source	Korea National Institute of Health(KNIH)
Method of Serialisation	GS1-128 code or EPC/RFID including GTIN, batch & expiry date. Serial data conform to timeline
Level of Serialisation	Item level (carton box)
Anti Counterfeit features	not yet specified
Deadline	1.1.2012 – Selected drugs must be printed with a serial number 1.1.2013 – All drugs must contain the expiry and batch information 1.1.2015 – All drugs must contain the serial number (Estimate) 2017 – aggregation in place

5.7. Japan

 Japan is planning a partial serialization on some products. They plan to use the GS1-DataBar or GS1-128 bar code for the serialised and non- serialised data.

“Health, Labour & Welfare Ministry / Federation of Pharmaceutical Manufacturers’ Associations of Japan”

Three packing units as targets of bar code indication:

- Individual Package (PTP sheet, Ampoule, Vial, etc.)
  GS1-DataBar (former RSS-Limited. RSS14 limited or stacked)
- Selling unit (minimum wholesale unit, e.g. box of 10 ampoules)
  GS1-DataBar (former RSS-Limited. RSS14 limited or stacked)
- Manufacturer’s Selling unit (Package of several selling units)
  GS1-128 bar code

5.8. Russia

 Russia proposed serialization with track and trace. 1D bar code with serial numbers provided by the government. The serial number is planned for each packaging level.

5.9. Serbia

 Serbia is undertaking a serialisation initiative.

5.10. Switzerland

 Is currently also looking at the introduction of serialisation and this is being piloted. Companies supplying into the Turkish market are investing in serialisation lines.

5.11. Turkey

 Turkey has unveiled product identification requirements that include a Data Matrix bar code with serialisation for prescription drugs, samples, hospital packaged products, formulas for medicinal purposes and over-the-counter drugs. The Turkish Ministry of Health had defined requirements, drafted guidelines, and identified specific industry standards to be used for items as well as transport packages (cases, cartons, etc.).

The ITS (Ilaç Takip Sistemi) as it is known was first due to be in place on January 1, 2009, but in the face of strong opposition was postponed until July 1, 2009 with an additional extension to the start of 2010, because pharmacies had not implemented the required technology in time. The system is now in place for carton level serialisation. As of July 1 2010, all pharmacists in Turkey's serialisation scheme (ITS) were officially unable to gain reimbursement for medicines which are not carrying the new 2D Data Matrix code.

Figure 47 – Typical ITS Print Layout

5.12. USA


As mentioned before, although an open ePedigree standard is ratified, the USA are some way from its adoption. This has resulted in revised legislation that states any manufacturer selling drugs in California must have an ePedigree for 50 per cent of its products by the start of 2015. The remaining 50 per cent must be designated an ePedigree before 1 January 2016.

Another wave of legislation comes into affect on 1 July 2016 prohibiting wholesalers or re-packagers from selling, trading, or transferring a dangerous drug without a pedigree. Also they cannot acquire a dangerous drug without receiving a pedigree.

The complete legislation will finally be implemented on 1 July 2017, when the measures affecting pharmacies come into force. These will then also apply the wholesaler and re-packager regulations implemented in 2016 to the pharmacies.

5.13. UK

No further details regarding the EU directive are currently known.

6. Overview of Legislative and Industrial Sector Organisations

A collection of organisation involved in the process of specification, standardisation or legislation for pharmaceutical anti-counterfeit strategies and pharmaceutical Track & Trace applications.

6.1. Anvisa

http://portal.anvisa.gov.br

The National Health Surveillance Agency was established by Law 9.782, of January 26, 1999. The Agency is designated an autonomous agency operating under a special regime. This means that ANVISA is an independently administered, financially-autonomous regulatory agency, with security of tenure for its directors during the period of their mandates. The Agency is managed by a Collegiate Board of Directors, comprised of five members.

Within the structure of Federal Public Administration, the Agency is linked to the Ministry of Health, under a Management Contract. The agency incorporated additional attributions: coordination of the National Sanitary Surveillance System (SNVS), the National Program of Blood and Blood Products and the National Program of Prevention and Control of Hospital Infections; monitoring of drug prices and prices of medical devices; attributions pertaining to regulation, control and inspection of smoking products; technical support in granting of patents by the National Institute of Industrial Property.

The institutional purpose of the agency is to foster protection of the health of the population by exercising sanitary control over production and marketing of products and services subject to sanitary surveillance. The latter embraces premises and manufacturing processes, as well as the range of inputs and technologies concerned with the same. In addition, the Agency exercises control over ports, airports and borders and also liaises with the Brazilian Ministry of Foreign Affairs and foreign institutions over matters concerning international aspects of sanitary surveillance.

6.2. Club Inter Pharmaceutique (CIP)

http://www.cipclub.org/

The Club Inter-Pharmaceutique (Inter-Pharmacy Club), an association regulated by the French 1901 law, seeks to improve the circulation of products and related information to serve the needs of public health.

Its mission is organized into 4 major areas:

- Coding
- Standardization
- Preparation of statistics
- Information to members

6.3. European Federation of Pharmaceutical Industries and Associations (EFPIA)

http://www.efpia.org/

The EFPIA is a Brussels-based trade union founded in 1978 representing the research-based pharmaceutical industry operating in Europe. Through its direct membership of 31 national associations and 44 leading pharmaceutical companies, EFPIA is the voice on the EU scene of 2,200 companies committed to researching, developing and bringing new medical treatments.

EFPIA Anti-Counterfeiting Group

The EFPIA AFC group consists of representatives from a number of large pharmaceutical companies, with expertise in intellectual property, security, packaging, distribution, and quality. In November 2010, the group published an update of the White Paper on The Anti-Counterfeiting of Medicines.

The paper attempted to:

- Influence the development of European legislation and encourage international collaboration.
- Define the role of suppliers, drug manufacturers, wholesalers, distributors and pharmacies in the fight against counterfeiting.
- Propose effective and affordable solutions for supply chain control.
- Recommend improved communications to the various stakeholders.

One of the key recommendations was the focus on 'Track and Trace Systems' at an individual pack level to identify the entry of counterfeits into the supply chain. The paper recommended the implementation of a pan-European bar code standard, based on the European Product Code (EPC).

6.4. Europe Taxation and Customs Union (TAXUD)

http://ec.europa.eu/health/index_en.htm

To guarantee the highest possible level of public health and to secure the availability of medicinal products to citizens across the European Union, all medicinal products for human use have to be authorised either at Member State or Community level before they can be placed on the EU market. Special rules exist for the authorisation of medicinal products for paediatric use, orphan medicines, traditional herbal medicines, vaccines and clinical trials.

6.5. GS1

http://www.gs1.org/

Founded in 1977, GS1 is an international non-profit association dedicated to the development and implementation98 of global standards and solutions to improve the efficiency and visibility of supply and demand chains globally and across multiple sectors. The GS1 System of standards is the most widely-used supply-chain standards system in the world. GS1's main activity is the development of the GS1 System, a series of standards designed to improve supply-chain management. The GS1 System is composed of four key standards: Bar codes (used to automatically identify things), eCom (electronic business messaging standards allowing automatic electronic transmission of data), GDSN (Global Data

Synchronisation standards which allow business partners to have consistent item data in their systems at the same time) and EPCglobal (which uses RFID technology to track an item).

The GS1 is registered as an issuing agency (ISO 15459).

6.6. Health Industry Business Communications Council® (HIBC)

http://www.hibcc.org

The HIBCC® is an industry-sponsored and supported non-profit organization. As an ANSI-accredited organization, the primary function is to facilitate electronic communications by developing appropriate standards for information exchange among all health care trading partners.

The broad mission has consistently expanded to meet industry requirements and has involved HIBCC in a number of critical areas, including electronic data interchange message formats, bar code labeling data standards, universal numbering systems, and the provision of databases which ensure common identifiers.

The current major activities have emerged as a result of this broadening focus:

- Standardized manufacturer, customer, and product identification codes, including the Labeler Identification Code (LIC), Health Industry Number (HIN®), and Universal Product Number (UPN®) and the Health Industry Bar Code (HIBC) Standards
- Computerized EDI protocols in ASC X12 approved message formats
- Participation in national and international organizations working to further enhance electronic communications standards.

Perhaps most important, HIBCC plays a major advocacy and educational role in the healthcare industry and serves as the forum through which consensus can be reached as we electronically transform ourselves for twenty-first century commerce.

The HIBC is registered as an issuing agency (ISO 15459), the registrated system identificator is “+”.

6.7. Informationsstelle für Arzneispezialitäten (IFA)

http://www.ifaffm.de/ **(in German only)**

The IFA works as a service provider for information regarding the German pharma market. The IFA is a common organization of pharmaceutical manufacturers (BP), pharmacies (ABDA) and pharmaceutical wholesalers (PHAGRO).

Currently, the IFA is responsible in Germany for the allocation of the "PZN" (central pharma number). Until now, the PZN has been marked on the medicinal product as a bar code but will be integrated into the 2D Matrix Code in the future. The IFA has thus applied for registration as so-called issuing agency (ISO 15459). In this way, the IFA will be one of the around 30 worldwide issuing agencies.

Web site: http://www.ifa-issuing-agency.org/de/home

6.8. securPharm

http://www.securpharm.de **(in German only)**

Specification for PPN-code http://www.ifa-coding-system.org/de/home **(in German only)**

6.9. Food and Drug Administration (FDA)

http://www.fda.gov/

The Food and Drug Administration (FDA or USFDA) is an agency of the United States Department of Health and Human Services, one of the United States federal executive departments, responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), veterinary products, and cosmetics.

6.10. International Federation for Animal Health Europe (IFAH)

http://www.ifaheurope.org/

IFAH-Europe is the federation representing manufacturers of veterinary medicines, vaccines and other animal health products in Europe. It represents both corporate members and national animal health associations in Europe. These associations comprise both local medium-size enterprises (SMEs) and international companies. IFAH-Europe's membership covers 90% of the European market for veterinary products.

6.11. Medicines and Healthcare products Regulatory Agency (MHRA)

http://www.mhra.gov.uk

The MHRA is the UK government agency which is responsible for ensuring that medicines and medical devices work and are acceptably safe. The agency was formed on 1 April 2003 with the merger of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA). It is an executive agency of the Department of Health.

6.12. Pharmaceutical Security Institute (PSI)

www.psi-inc.org

Most Pharmaceutical Companies also belong to the Pharmaceutical Security Institute (PSI) which is a multinational, non-profit making organisation dedicated to:

- Protecting the public health.
- Sharing information on the counterfeiting of pharmaceuticals.
- Initiating enforcement actions through the appropriate authorities.

PSI was established in 2002 by the security directors of 14 major pharmaceutical companies. It is based in Washington DC but with a European regional office in London. PSI works closely with international police organisations, custom and excise groups, and Regulatory Agencies to gather statistics on counterfeiting activities, which are shared with its members.

7. Guidance to finding a Reliable Partner

With the current situation of some regulatory uncertainty, technological development and infrastructure requirements, early adopters have established strong relationships with reliable suppliers who can help manage costs and minimise risks.

7.1. Questions to ask your Potential Supplier

Some of the points which need consideration include:

- Is the supplier able to supply solutions using proven systems and technologies, possibly already in use on your production line? This could represent significant savings in the long term.
- Does the supplier have financial stability and sufficient resources to meet the immediate requirements and to deliver a proficient service in the long-term?
- How well informed is the supplier with the current regulatory requirements? This is important for two reasons:
- To ensure the necessary functionality is available in the current solution and also ensures that the supplier understands the future requirements as they evolve.
- In order to be able to create the documentation necessary to satisfy the regulatory authorities that a pragmatic approach have been made to the validation of the system.
- Has the supplier demonstrated the overall strength needed to meet the requirements? Does he have the resources in development, project planning, manufacture and integration of third party products in order to reach the goals?
- Does the supplier have a global service and support network, which is strategically located for rapid response when needed?

8. Appendix

8.1. Glossary of Terms

A

Aggregation - Aggregation refers to the requirement by the manufacturer to serialise each drug packaging unit (or unit of sale) with a unique identity with the creation and recording of incremental parent-child associations at each subsequent stage of packaging - bundles, cases and pallets. These associations enable single scans of pallets or shipping cases to capture the detail of all units contained within, thereby forming the basis of the e-pedigree documentation for the batch.

Authentication - Authentication is the process of verifying that the number on the drug package is genuine and originated from the authorised pharmaceutical manufacturer. Authentication uses the unique product serial number information stored on a RFID tag or bar code on a drug's packaging, at the unit of sale level, so that it can used by wholesalers and pharmacies to verify the integrity of the drug package.

B

BCR - Bar code Reader (or Scanner). Device used to manually or automatically read a bar code.

C

Calibration - Documented comparison, by written and approved procedures, of a traceable measurement standard, of a known accuracy, with another measuring device to respond to, detect, correlate, report or eliminate any variation in the accuracy of the item being compared over an appropriate range of measurements.

Carton - Cardboard container for drug product and patient information leaflet, sometimes referred to as a 'folding box'.

Case - Outer container for cartons or bundles of cartons, sometimes referred to as a 'grouping box'.

CFR - Code of Federal Regulations, the code of general and permanent rules and regulations published in the Federal Register by the executive departments and agencies of the Federal Government of the United States. Part 21 is handled by Food and Drug Administration. Part 11 defines the criteria under which electronic records and electronic signatures are considered to be trustworthy, reliable and equivalent to paper records.

cGMP - Current Good Manufacturing Practice.

D

Data Matrix code - is a two-dimensional matrix bar code consisting of black and white 'cells' or modules arranged in either a square or rectangular pattern.

E

EFPIA - European Federation of Pharmaceutical Industries and Associations represents 31 national pharmaceutical industry associations and 44 leading pharmaceutical companies operating in Europe.

End User - Economics and commerce define an end-user as the person who uses a product.

ePC - Electronic Product Code is a family of coding schemes created as an eventual successor to the bar code. The EPC was created as a low-cost method of tracking goods using RFID technology.

EPCGlobal - is a joint venture between GS1 and GS1 US. It is an organisation set up to achieve world-wide adoption and standardisation of Electronic Product Code technology in an ethical and responsible way.

e-pedigree - An electronic pedigree is a legal chain of custody record that traces a drug from the manufacturer to the pharmacy and contains information about all transactions involving that drug.

ERP - Enterprise Resource Planning - A computerised system for integrating company-wide data in order to improve planning activities, provide better control of operations, and enable products to get to market more quickly.

F

G

GAMP - Good Automated Manufacturing Practice is developed and controlled by a technical sub-committee, known as a COP (Community Of Practice) of the International Society for Pharmaceutical Engineering (ISPE). The goal of the community is to promote the understanding of the regulation and use of automated systems within the pharmaceutical industry.

GMP - Good Manufacturing Practice is that part of quality assurance that ensures that products are produced and inspected uniformly in accordance with the quality standards and which conform to their intended use and the approval documentation.

GS1 - Founded in 1977, GS1 is an international not-for-profit association dedicated to the development and implementation of global standards and solutions to improve the efficiency and visibility of supply and demand chains globally and across multiple sectors. The GS1 System of standards is the most widely-used supply-chain standards system in the world.

GTIN - Global Trade Item Number is an identifier for trade items developed by GS1. Such identifiers are used to look up product information in a database which may belong to a retailer, manufacturer, collector, researcher, or other entity.

H

I

L

M

Marking - Information about the contents and shipment of a package which is printed on or affixed to the surface of the package.

MES - Manufacturing Executing System manages and monitors work-in-process on the factory floor including labor and production reporting, as well as on-line inquiries and links to tasks that take place on the production floor. Manufacturing Execution Systems may include one or more links to work orders, receipt of goods, shipping, quality control, maintenance, scheduling or other related tasks.

MRP - Manufacturing Resource Planning. An automated system for handling information directly relating to manufacturing, this includes inventories, bills of materials (BOM) and orders from purchasing.

MRPII - Manufacturing Resource Planning II. An expanded version of MRP that includes enhanced capacity for planning and scheduling the use of manufacturing resources.

N

NDC - National Drug Code. The drug identification code used in the USA, similar to the European GTIN.

O

OCR - Optical Character Recognition is used in pharmaceuticals to denote checking of text but using a specific font of characters.

OCV - Optical Character Verification is used in pharmaceuticals to denote checking of text by ‘show and go’ operation, without a pre-trained font of characters.

P

Package - The completed product of a packing operation. It consists of the packaging and its contents prepared for shipment.

Packaging - Assembly of one or more containers, and any other components, which are necessary to ensure compliance with minimum packaging requirements of applicable regulations.

Packing - The art and operation by which an article, material, or substance is enveloped in a wrapping and/or packaging or otherwise secured.

Physical security - features are substances or products which are introduced into, or attached to packaging materials and/ or products. The presence of these security substances is verified to authenticate the protected item. As the manufacturing process of security products is secret and its availability strictly limited, it is very difficult to counterfeit products secured in this way.

Procedure - An approved document listing a specific set of instructions which, when followed, will produce a product or result defined by a specification. Procedures are used to define and control the manufacture of materials as well as the operation and/or maintenance of equipment, systems or processes.

Production - All activities subsequent to design transfer up to the point of distribution.

Programming - Coding of program modules that implement a design.

Protocol - The written and approved document of an experimental sequence of tests that, when executed as prescribed, are intended to produce documented evidence that the equipment or system does what it is designed to or claims to do reproducibly.

Q

Qualification - Used to describe the *Testing* and review of a piece of equipment, system or sub-system of a process to assure its fitness for use. *Qualification* deals with components or elements of a process, while *Validation* deals with the entire manufacturing process for a product.

Quality System - All planned and systematic activities necessary to provide adequate confidence that a product, process or service will satisfy given quality requirements.

R

Random Serialisation - Printing or marking of data on every pack, where one element of the printing contains a code who's value is random and non-sequential.

RX - Prescription drugs (medication)

S

Serialisation - Serialisation refers to a numerical system that assigns a unique number or identification code to each packaging unit. A serialisation scheme is built around a code structure that typically identifies the manufacturer, the product type, and each specific item unit.

sNDC - Serialized National Drug Code. The proposed scheme for serialisation using an SNI with the additional National Drug Code (NDC) identifier added.

SNI - Standardised Numerical Identification - the name given to the serialization component in the USA.

T

T&T - Track-and-Trace is the process of pack marking and aggregation in marked bundles, cases and pallets that produce the product required for the track and trace environment.

U

UID - Unique identification.

URS - User Requirement Specification - a list, often comprehensive describing the user requirements for a project.

USC - Unique Serial Code - a unique alphanumerical non sequential code, created by a Code Number Generator. It can be applied to a carton, to a bundle of cartons, to a case of bundles, to a pallet of cases and so on. It allows to uniquely identifying a product in the complete supply chain.

V

Validation - The overall term for the establishing of documented evidence through defined tests and challenges, that a system, manufacturing process, analytical method and/or piece of equipment meets design criteria and that adequate provisions have been established to keep it in a *State of Control* so it will produce a product that meets predetermined specifications and quality attributes.

V-Controller - Verify Controller. Real-time software that controls the verifying device.

X,Y,Z

XML - Extensible Markup Language - it is a general-purpose specification for creating custom markup languages. It is classified as an extensible language, because it allows the user to define the mark-up elements. XML's purpose is to aid information systems in sharing structured data, especially via the Internet, to encode documents, and to serialise data.

8.2. Index of Figures

8.3. Index of Tables

8.4. Overview of EU Countries

State – November 2011

Name	ISO 3166 Country Code
Austria	AT
Belgium	BE
Bulgaria	BG
Cyprus	CY
Czech Republic	CZ
Denmark	DK
Estonia	EE
Finland	FI
France	FR
Germany	DE
Greece	GR
Hungary	HU
Ireland	IE
Italy	IT
Latvia	LV
Lietuva	LT
Luxembourg	LU
Malta	MT
Netherland	NL
Poland	PL
Portugal	PT
Romania	RO
Slovakia	SK
Slovenia	SI
Spain	ES
Sweden	SE
United Kingdom	GB

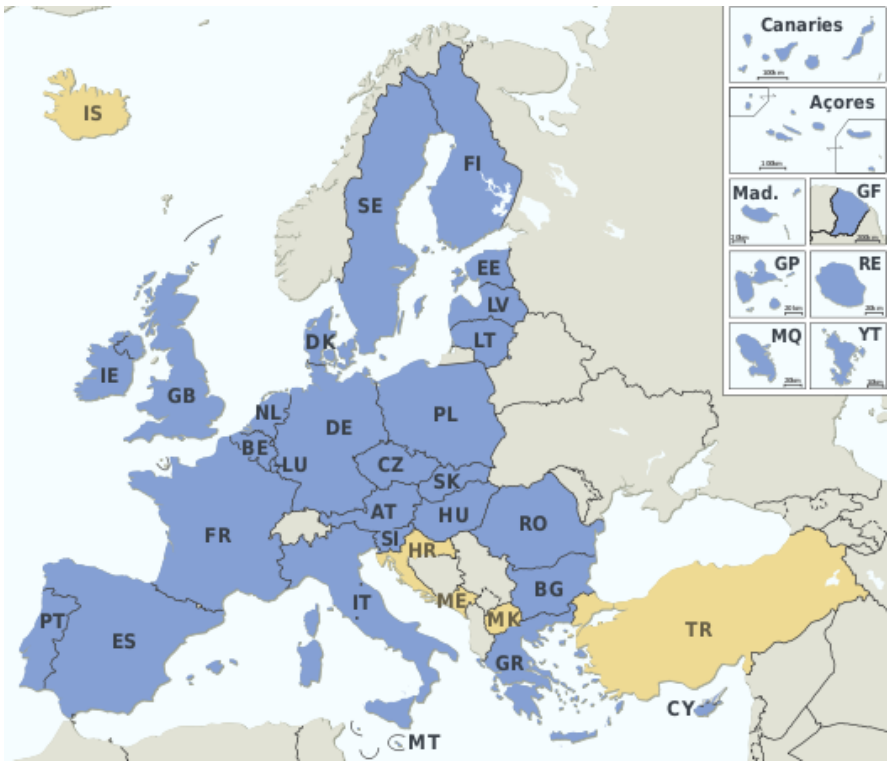


Table 8 - EU Countries [16]

Planned new member in 2013 - Croatia.

[16] *Source - Wikipedia*