Pharmaceutical Regulatory Affairs: Open Access

Rampinelli and Argenta, Pharmaceut Reg Affairs
2016, 5:1
DOI: 10.4172/2167-7689.1000160

Case Report Open Access

# Different Approaches and Timeframes in Anti-Counterfeiting Medicinal Products: Europe vs. United States

**Rampinelli P and Argenta G***

*Universita degli Studi di Bologna, Bologna, Italy*

***Corresponding author:** Argenta G, Universita degli Studi di Bologna, Bologna, Italy, Tel: +393288787312; E-mail: guido.argenta@europe.com

**Received date:** February 01, 2016; **Accepted date:** February 04, 2016; **Published date:** March 09, 2016



**Abstract**

Tracking and tracing pharmaceutical products is a key element of any effective solution to the problem of counterfeit medicines.

This paper aims to provide an updated assessment of the timeframes for implementing the European medicinal trace-and-trace system in the wake of the delays and uncertainties that stand in the way of meeting the deadlines proposed at the end of 2007.

Across the USA, federal and state laws advocating ePedigrees (RFID) have been proposed and enacted to address the criminal activities and increasing threats to public health posed by counterfeit drugs.

In order to implement the EU Directive, stakeholders have agreed to develop and implement an "end-to-end" concept aiming at verifying the packaging of medicinal products using a Data-Matrix Code.

**Keywords:** Pharmaceutical tracin; Directive 62/2011/EU; Falsified; Counterfeit; Data matrix; RFID

## Introduction

Counterfeiting is a major problem in the global healthcare system. It increasingly affects the developed world as well as the developing world. Tracking and tracing of pharmaceutical products is a key element in an effective solution to the problem of counterfeit medicines. Europe-wide action will be needed to create an efficient and workable system, which will need to be backed up with parallel initiatives, such as increased criminal enforcement and penalties, and stricter rules on repackaging. There is already an established legal basis which would permit an EU-wide solution. It is now up to industry, governments and the European Institutions to use these powers and put in place an effective track-and-trace system [1].

This paper aims to provide an updated assessment of the timeframes for implementing the European medicinal trace-and-trace system in the wake of the delays and uncertainties that stand in the way of meeting the deadlines proposed at the end of 2007.

In addition, the systems under examination by European member states are compared to the one adopted by the US.

## Background

Directive 2011/62/EU introduced anti-counterfeiting legislation on medicinal products, amending a previous Directive 2001/83/EC to include new regulations, to be implemented within specific timeframes by means of delegated acts, a new category of legal act sanctioned by the Lisbon Treaty [2-4].

Already in 2006 DG Enterprise and Industry had presented policy and administrative guidelines aimed at fighting the counterfeiting of medicinal products. During the same period an independent body, Europe Economics, presented an authoritative report on the issue. The report outlined the need "to trace each pack and perform authenticity checks. This could be attained by a mass serialisation feature on the outer packaging. Technical details would be further defined in implementing legislation and / or by standardization organizations" [5,6].

From 2007 the European commission itself conducted several adhoc studies on the negative social and economic impact, in terms of monetary and health costs of falsified medicines entering the legal supply chain. Impact Assessment SEC 2008, 2674 (Staff Working Document) Annex-6 was one of the documents presented along with the proposal that was subsequently to become Directive 2011/62/EU.

### Summary of European medicinal products anti-counterfeiting law: Directive 2011/62/ EU

The directive's provisions can be summed up as follows:

- Far-reaching measures to guarantee GMP and GDP.
- End-to-end supply-chain control measures to ensure distribution chain transparency.
- Tighter checks and inspections, especially in third countries (API – GMP).
- Safety features (compulsory for prescription drugs considered at risk, and in exceptional cases also for OTC medicines (discussion still on-going).
- No absolute ban on repackaging; parallel trade possible.
- On-line pharmacies require a specific logo and must obtain special authorization from the competent authorities.

- Quality requirements for excipients.
- Definitions: the term "falsified medicinal product" does not include "unintentional manufacturing errors".
- GMP (Good Manufacturing Practice).
- GDP (Good Distribution Practice).
- API (Active Pharmaceutical Ingredients).

The European definition of falsified medicinal products is any medicinal product with a false representation of:

(a) Its identity, including its packaging and labeling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients.

(b) Its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorization holder.

(c) Its history, including the records and documents relating to the distribution channels used.

This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights.

Interesting to note: "The term falsified medicinal product implies something quite different from the phrase: Infringements of intellectual property rights in its full meaning".

More specifically, the subject of this paper, Directive 2011/62/EU requires that medicinal products at risk of falsification bear 'safety features'. With the exception of radiopharmaceuticals, the outer (or immediate) packaging of specified medicinal products must have safety features that allow wholesale distributors and authorized dispensers to the public to identify and verify the authenticity of each individual pack. In addition, the outer packaging must be 'tamper-evident' i.e., have a safety feature or design able to detect evidence of tampering (e.g. a torn label or unsealed cap). In fact, while tamper detection systems have long been used by the industry, they have failed to reduce counterfeiting significantly. This is because although tamper-evident systems successfully detect whether a pack has been tampered with, they are easily copied by counterfeiters.

**Delegated act on preparation safety features:** The European commission is tasked by the European Parliament and Council with drafting and implementing delegated acts that detail the specific safety features required on the individual packs and outer packaging of medicinal products to comply with Article 54, letter of the Directive 2001/83/EC (as modified by Directive 2011/62/EU), in accordance with Articles 121a, 121-b and 121c of the same Directive [7].

Before issuing the provisions however, the commission which enjoys ample autonomy in the adoption of delegated acts can to seek the opinion of stakeholders through a transparent consulting procedure. The various solutions put forward as safety features are still undergoing this process of approval. In addition, the commission must also evaluate the medium / long term advantages of the system most suitable to ensure greater supply-chain safety and weigh them against the economic burden required of industry firms and operators to adopt it. The commission concept paper submitted for public consultation (18/11/2011 Sanco ddg1.d. 3 (2011) 1342823) indicates the adoption of delegated act as scheduled for 2014 (pt. 7) and invites stakeholders to comment on the consultation paper by 27 April 2012 at the latest.

The associations representing the drug manufacturing industry, EUCOPE and EPFIA, are anxious to keep down the cost of introducing the new system.

EUCOPE, for example, advises against making it obligatory to include the batch number and expiry date on the Unique Identifier on the grounds that the "inclusion of the expiry date and the batch number would neither be in line with the principle of cost-effectiveness nor serve as a benefit for patient safety [8]."

It should be pointed out however, that in an end-to-end system expiry date and batch number information would provide numerous advantages for medicinal product management at the pharmacy or dispensing point.

"The magnitude of the benefits that could be credibly attributed to the proposed counter- measures depends on the assumed counterfactual the extent to which counterfeit medicines are already penetrating the EU market, and the rate at which this would grow, in a business- as-usual scenario."

(a) An "optimistic" base case: the EU market share of counterfeit medicines was one-half per cent in 2005, and would remain at that level.

(b) A "pessimistic" base case: the EU market share of counterfeit medicines was one-half per cent in 2005, and is growing by 10% a year.

In the "optimistic" case, which implies that there are many more counterfeits in the EU legitimate supply chain than have been identified, it would be a realistic target to eradicate counterfeit medicines from the legitimate supply chain by 2015. In the "pessimistic" base case, it would be more realistic to consider containment at 2011 levels. These two cases are illustrated below as the "optimistic-eradication" and "pessimistic-containment" scenarios respectively (Figure 1).

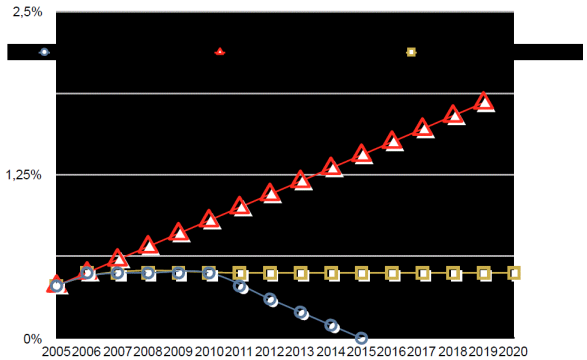


**Figure 1:** Market share scenarios: Optimistic-eradication and pessimistic-containment.

## Timelines

**2 January 2013:** Dir. 2011/62/UE - transposition requirement at national level.

**2014:** Publication of the delegated acts (prevision).

**2017:** The provisions in the delegated acts should be enforced at national level within 3 years of their publication.

**2023:** Member states which, on 21 July 2011, already have safety systems in place (….) shall apply the provisions (…) at the.

The timelines for the transposition and implementation of safety features are difficult to foresee for many European countries, including Italy. The calendar set down by Article 4 of Directive 2011/62/EU gives 2 January 2013 as the deadline for transposition of its provisions, while publication of the delegated acts should be completed by 2014. Art. 2, §2 of the Directive also lays down that the provisions in the delegated acts should be enforced at national level within three years of their publication and that "member states which, on 21 July 2011, already have safety systems in place (….) shall apply the provisions (…) at the latest from 6 years after the date of application of the delegated acts (…)".

The European procedure is therefore scheduled for completion in 2017. Uncertainties abound however, as to its application in the individual Member States in view of the fact that some countries, including Italy, already have safety systems that must be made compliant "at the latest from 6 years after the date of application of the delegated acts" in other words by 2023.

It should be recalled that simply transposing Directive 2011/62/EU into the individual national legal systems is not sufficient since the Directive merely sets down general goals and does not enter into details of the procedures and instruments to achieve them, this being left to delegated acts which should be adopted by member states by 2017.

Despite the strict obligation to implement the above mentioned safety features by 2023, forecasting any exact timeframe within which the various countries are likely to comply is an arduous task.

It is generally believed that adoption timeframes will not so much depend on the automatic mechanisms already in place to introduce community law into the various national legal systems as on the political will in the individual countries to progress enforcement.

It cannot be excluded therefore that anti-counterfeiting measures regarding medicinal products laid down by the European Union will become operational only after 2023.

A unique identifier for Europe: RFID or data matrix?

The unique identifier is a device applied to each individual pack of pharmaceutical products that a pan-European control system will be able to recognized anywhere in the EU, tracing the product's path from manufacture through to delivery to the end user. Various track and trace methods have been examined in Europe, in particular the data matrix code and the RFID (radio frequency identification) systems.

In May 2009 at a conference on a project to identify and trace medicinal products in compliance with EU requests, the European federation of pharmaceutical industries and associations (EFPIA) presented the results of investigations into the two systems able to meet EU traceability requirements: the above mentioned RFID and data matrix systems. The EFPIA proposed a common European mass serialization and traceability standard, i.e. the two-dimensional data matrix bar code, called the 2D data matrix ECC 200 able to contain the following information: product code (GTIN), serial number (Ser), expiry date, batch code and a series of other information. Data matrix is a small, low-cost device compatible with the control systems already installed.

In contrast, the American Food and Drug Administration (FDA) had, as early as 2004, proposed that the Radio Frequency Identification system be adopted also by Europe to control medicinal products in the legal supply chain. RFID technology allows automatic identification by means of radio frequencies that interact with a microchip (also called a 'tag' or 'transponder') placed on the pack. The identification code is read indirectly by a wireless device, a feature that greatly facilitates warehousing and storage operations. Radio frequency technology does, however, have some drawbacks. There is no standard RFID device and liquids and metals may interfere with the system's ability to read the information on the microchip [9]. An investigation carried out by the Italian consortium DAFNE in 2008 underlined that 'products with metal primary packaging, such as aerosol cans or blister packs, do not appear problematic if there is an air gap between packages, even if small; if in other words, the pallet is able to 'breathe'. However, in the absence of an air gap and with tightly packed product, device reading capability falls considerably [10] (Table 1).

| Linear Barcode, Data Matrix, RFID Comparison | | | |
|---|---|---|---|
| **Characteristics** | **Linear Barcode** | **Data Matrix** | **RFID** |
| Scanning technology | Can be automatic system but the device must be read directly by a scanner. | Can be automatic system but the device must be read directly by a scanner. | Indirect automatic reader system. |
| | 1D traditional linear bar co- des can only be read by scanning from left to right with a laser beam. | 2D matrix code can be read at any angle of rotation or 60 degrees skewed with a CCD camera. | RFID tags can make their presence known to readers. No need to have direct line of sight with reader. |
| | | There must be a direct line of sight between the Data Matrix and the scanner. | |
| Identification | Read only (reports initialized information only) | Read only (reports initialized information only) | Add / change or store data |
| Read Range | 1" to several inches (short range only) | 1" to several inches (short range only) | 1" to 100's of feet or more |
| | | | (short range to long distance) |
| Read Rate | Few labels at a time (requires manual orientation) | Only a few labels at a time (usually requires manual handling or orientation) | Several tags can be read simultaneously (up to 1,000's in seconds) |

| | | | |
|---|---|---|---|
| Durability | Easily warped because of exposure to the "elements" – Removed / Tarnished (must be external) | Easily warped because of exposure to the "elements" – Removed / Tarnished (must be external) | Rugged and well protected (can be sub-surface in many applications) |
| Security | None. Easy to reproduce. | Cryptographic systems do exist but have not been designed for large-scale use. | A series of information encrypting measures making falsification more difficult. |
| Cost (€) | 1-10 cents per label. | 1-10 cents per label. | Currently 10-20 cents per label. |
| | Virtually no cost if printed on packages. | | RFID tag. |
| | | | Also more in some cases. |
| Type of Tracking | None | "End-to-End" | "E-pedigree" |
| | | Labels registered in on-line database and checked at point of delivery. | RFID tag read at every level of the pharmaceutical chain. |

**Table 1:** Linear barcode, data matrix, RFID comparison.

Despite this, RFID can very reasonably be expected to arouse much interest in the logistics industry since it would allow wholesalers to scan pallets swiftly and efficiently. In 2010 the EPFIA financed a pilot project in Sweden aimed at assessing the appropriateness of the second system: Data Matrix. 25 pharmacies were recruited for a period of four months during which 25,000 packs were checked and scanned. The system effectively identified not only falsified medicines but also picked up expired or about-to-expire packs. Moreover the pharmacists involved in the pilot project were not inconvenienced by having to use the scanning system, which fitted easily into their work routine "The model works in practice" [11]. The data matrix track-and-trace system examined by the European definition of falsified medicinal product: EFPIA was able to ascertain the authenticity of the medicinal products right to the point of dispensation. Products are serialized individually and registered with an on-line database, or repository, by manufacturers. Pharmacies at the end of the supply chain log into the central repository and verify the code data on the product with the data registered by the manufacturer, checking that:

- The product record corresponds to the data on the product.
- The product record does not indicate that the product has already been dispensed;
- The product record does not contain any special notices or warnings [12].

## FDA's choice

After a trial period, in 2007 the FDA adopted RFID track-and-trace technology as its standard for the entire pharmaceutical supply chain [13].

Manufacturers register the code of each medicinal product in an online database, or repository. Subsequently, all other operators along the supply chain check the data on the same medicinal product and record all handling and commercial transactions are pertaining to it. Any discrepancy in the online data string could indicate that the medicinal product has been illegally introduced into the supply chain.

RFID tags have the advantage of allowing direct, uninterrupted data transmission even in the absence of a direct line to the reader. However, although defined by some "a key to automating new technologies often promise more than they can really offer everything" RFID is no exception.

Nor does RFID technology seem to be eclipsing barcodes in Europe. Many European bodies, agencies and organizations are reluctant to change technology. The barcode has been widely used for several decades and data matrix is the latest generation. EFPIA even undertook an independent pilot study to underline and confirm the validity of the data matrix system. Some manufacturers have, however, acted independently [14].

In an attempt to protect probably the most falsified medicinal product in the world, Viagra, Pfizer has applied RFID labels to all packs destined for the US market.

Of note is the fact that although Europe is a leader in RFID R&D with annual growth rates of approximately 45% thanks to European research programmes, the European market for the system lags considerably behind the rest of the world where growth rates are around 60% [15].

## European commission and stakeholders

In 2006 the European commission conducted a public consultation on RFID technology and on 15 March 2007 published a report entitled "an efficient, safe and 'privacy-preserving' Approach to RFID Technology" [16].

Both the commission and the pharmaceutical industry believe that this technology has great potential to increase patient safety and quality-of-care as well as improve logistics in the supply chain of EU countries. Nonetheless the consultation on the Unique Identifier concluded on 27 April 2012 showed that most pharmaceutical industry representatives preferred the data matrix system because it entails lower costs and is compatible with existing systems. Article 4 of Directive 2011/62/EU establishes that the commission must carry out a final assessment to review the benefits, costs and cost effectiveness of a proposed system before it is definitively adopted with a delegated act. For this purpose the Commission has engaged in intense consultations with stakeholders.

Indeed, even if so-called 'Comitology' is no longer provided for by the treaty of Lisbon, it is likely that the commission will continue to make wide use of consultation given the experience it affords.

Consultations are necessary because the information and figures given in the initial impact assessment accompanying a draft Directive could in the meanwhile have become obsolete and require updating. In

fact the length of time elapsing between the preparation of a piece of community law and the adoption of the pertinent delegated acts has been widely criticized. It should, however, be remembered that if those impacted by new legislation are to be guaranteed certainty in law, the commission is duty bound to define accurately the technical details contained in subsequent delegated acts.

In addition, to complete the framework of a fundamental piece of legislation, the Commission needs the contribution of experts and stakeholders in the field to gather information from real life situations and carry out studies.

Interestingly, most stakeholder replies to the public consultation on safety features underlined a preference for data matrix (Table 2).

| Stakeholder | Data Matrix | RFID |
|---|---|---|
| ABDA Federal Union of German Associations of Pharmacist | "Considering technical standards the ABDA clearly prefers concept no. 2 (2D data matrix Code)". | RFID is relatively untested<br>RFID is ruled out regarding a higher drug safety. RFID is "expensive and possibly unsafe" |
| Actavis | "Strongly Support EGA position" | "Strongly Support EGA position" |
| ABPI Association of the British Pharmaceutical Industry | "The implementation of the 2D-matrix barcode, and the information within it, is in the interest of a number of stakeholders" | "AESEG considers RFID is not an option because of the higher costs and the technical imperfections. RFID will also not increase patient safety" |
| Assogenerici | "The ASSOGENERICI considers it is sufficient to have a linear barcode to be in line with the scope of the Directive" | "The ASSOGENERICI considers RFID is not an option because of the higher costs and the technical imperfections. RFID will also not increase patient safety" |
| EGA European Generics Medicine Association | "The EGA considers it is sufficient to have a linear barcode to be in line with the scope of the Directive" | "The EGA considers RFID is not an option because of the higher costs and the technical imperfections. RFID will also not increase patient safety" |
| EPFIA European Federation of Pharmaceutical Industries and Associations | "EFPIA supports the position set out in the joint response in favour of the Data Matrix code" | Not mentioned |
| EUCOPE European Confederation of Pharmaceutical Entrepreneurs | "The 2D-Barcode seems to be the most realistic and cost-effective option because 2D Barcodes are already widely used in the pharmaceutical industry" | "EUCOPE considers RFID not an option because of the higher costs, data security issues and the technical imperfections. RFID would be expensive because a microchip would have to be embedded in the pack" |
| Farmindustria | "At the moment this is the best solution because can hold a lot of information, it's applicable to small packs and this not too expensive" | Expensive solution and possibility that this technology interferes with some materials, aluminum and glass so the reading of serial number not possible |
| PHAGRO German Association of Full line Wholesalers | "PHAGRO supports a 2D-Bar Code holding the information related to each single pack (product code, batch number, expiry date, a unique randomized serial number and where necessary the national product number)" | Not mentioned |
| EAEPC-EFPIA-GIRP-PGEU Joint Response | "The only reasonable, cost-effective, technical solution is to adopt the 2D barcode, i.e., a Data Matrix code, as the data carrier" | "Given the current state of RFID technology, the ESM stakeholders do not believe it is the appropriate technology […]" |
| Responses to the public consultation on the concept paper on the detailed rules for a unique identifier for medicinal product for human use<br>http://ec.europa.eu/health/human-use/falsified_medicines/developments/2012-06_pc_safety-features.htm | | |

**Table 2:** Data matrix.

The replies to the public consultation were uniformly 'standard' even if in many cases no in- depth analyses of RFID technology issues were carried out. It would appear that stakeholders had formulated a common opinion among themselves in anticipation of the consultation with a view to providing a clear indication to the commission.

Those consulted expressed the view that RFID technology (already adopted by the FDA) was 'too costly' and had 'technical imperfections'. Opinions were often expressed using exactly the same wording.

## Conclusion

It seems almost inevitable that the data matrix system will be adopted since it is less expensive and can be adapted to existing systems in member states, and this despite an awareness that very probably the RFID system is intrinsically transnational, and even if initially more expensive, would be the best system in the long-term, not least because costs continue to fall. European stakeholders have, however, preferred to opt jointly for a common 'safer' approach. Moreover good results will certainly be obtained with the data matrix system in terms of curtailing the entry of falsified medicines into the legal supply chain. However, adopting the same system as the USA would have given the European Union broader advantages. RFID technology has already proved a useful and practical tool to reduce the risk of practitioner error. It is also proving to be a highly effective means of contributing to the development of better public health management systems [17]. Now was the ideal moment to build up a global harmonized approach.

In any event, the "Joint Response (EAEPC-EFPIA-GIRP-PGEU)" has not discarded RFID tracking. According to stakeholders, the technology is not yet ready but in the future could flank the data matrix system [18].

It is however, puzzling that all stakeholders rejected RFID technology without conducting tests. This was not the case for the data matrix system, which was assessed and widely approved.

Enforcement timeframes in the individual EU member states remain uncertain. It is unlikely that an all-embracing European protection network will be in place before 2023, the adoption of the delegated act being scheduled for 2014 [19].

Nor is it far-fetched to predict that Europe will be in a position to effectively protect its pharmaceutical supply chain only around 2030.

## References

1. Killick J, Herzog DS (2007) Tracking and Tracing Pharmaceutical Products in the EU: A Key Element in the Fight against Counterfeit Medicines.
2. Directive 2011/62/EU of the European Parliament and Council of 8th 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. Official Journal of the European Union 174-187.
3. Directive 2001/83/EC of the European Parliament and Council of 6th November (2001) The Community code relating to medicinal products for human use.
4. Tizzano A (2012) "Codice dell'Unione Europea" (5th edn.) Cedam.
5. European Commission DG Enterprise and Industry.
6. Policies to Combat Counterfeit Medicines Contribution to Impact Assessment (2008) Europe Economics Chancery House.
7. http://ec.europa.eu/health/files/counterf_par_trade/planning.pdf
8. EUCOPE (2011) Public Consultation on the Delegated Act on the Detailed Rules for a Unique Identifier for Medicinal Products for Human Use and its Verification. Sanco.ddg 1D 3: 342823.
9. EFPIA (2009) Project for Coding and Identification of Pharmaceutical Products in Europe- Plan for a pilot trial.
10. http://www.consorziodafne.com
11. EFPIA Product Verification Pilot (2010) Joint Final Report.
12. EFPIA (2012) Coding and Identification of Products: towards safer medicines supply.
13. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108668.htm
14. Want R (2008) "RFID: A key to Automating Everything" Scientific American.
15. RFID chips (2006) Future technology on everyone's lips – Deutsche Bank Research.
16. http://ec.europa.eu/health/files/falsified_medicines/2012-06_safety-features/assogenerici_en.pdf
17. Buscemi A, Carraro A (2011) "L'innovazione tecnologica RFID a garanzia della sicurezza del Paziente". Dir San Mod 59: 1–12.
18. Coding and Serialisation (2012) Concept Paper submitted for Public Consultation. Joint Response (EAEPC-EFPIA-GIRP-PGEU).
19. Delegated Act on the Detailed Rules for a Unique Identifier for Medicinal Products for Human Use and its Verification (2011) Concept Paper Submitted.