The Implementation of the Data Matrix System for Medicinal Products for Human Use in France and the EU Context

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Since the 31st of December 2010 two-dimensional ("2D")-barcodes, Data Matrix, have replaced the former barcode and are mandatory on the outer-packaging of medicinal products for human use in France. The Data Matrix system, combined with batch-traceability, is already used for animal health products in France[1]. The measure is applicable to all medicinal products having a marketing authorization in France and is combined with a progressive switch of the marketing authorization number and the inclusion inter alia of the batch-number in the 2D-barcode. It aims at facilitating batch-recall and securing the supply chain. No serialization is planned for the moment by the French health regulatory authorities but it may evolve with future anti-counterfeiting measures, especially as a requirement resulting from the future adoption of the European Commission directive on the prevention of falsified medicinal products entering the legal supply chain[2].

1. The Regulatory Framework

The obligation to print a 2D-barcode (Data Matrix system) on the outer-packaging of medicinal products for human use was enacted by the French Medicines Agency ("AFSSAPS") in March 2007 and took effect from the 31st of December 2010 onwards[3]. It concerns all medicinal products for human use with a marketing authorization in France irrespectively of their prescription status. The notice foresees firstly the switch of the marketing authorization number with 7 digits ("CIP 7 code") to a market authorization number with 13 digits ("CIP 13 code")[4] due to the coming saturation of the CIP 7 code. Germany is facing the same issue with its product number, the Pharmazentralnummer (PZN). In France however the CIP code corresponds not only to the product number but also to the marketing authorization number. Corresponding to the schedule foreseen in the notice, the publication of the CIP 7 code and the CIP 13 code switch codes already began in the first quarter of 2007 and the allocation of the CIP 13 code alone (without the CIP 7 code) has been implemented since January 2009.

Secondly, the mandatory implementation of the Data Matrix labeling for all medicinal products is foreseen from the 31st of December 2010 onwards[5]. The first batch with Data Matrix labeling was planned to exit production lines on the 1st of January 2008 with the objective that on the 31st of December 2010 all batches exit production lines with Data Matrix labeling system[6]. Specific provi-

[1] See Decree from the 20. 03. 03, O.J. of the 22. 03. 03, *http://admi.net/jo/20030322/SANP0320072D.html.*

[2] Proposal for a directive of the European Parliament and of the Council amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of medicinal products which are falsified in relation to their identity, history or source (COM (2008) 668) of 10. 12. 2008: *http://ec.europa.eu/health/human-use/package_en.htm.*

[3] See «Avis aux titulaires d'autorisation de mise sur le marché de médicaments à usage humain et aux pharmaciens responsables des établissements pharmaceutiques mentionnés à l'article R. 5124-2 CSP (1)», AFSSAPS, O.J. of 16. 03. 07, *http://admi.net/jo/20070316/SANM0720920V.html.*

[4] See Point 2 of the notice.

[5] Parallel to the implementation of the Data Matrix, the GS1 128 coding replaces the linear barcode 39.

[6] See Point 3 of the notice.

sions have been provided by the AFSSAPS[7] for solutions for parenteral use and for medicinal products without outer-packaging.

Finally, the notice provides for mandatory batch-traceability[8] for all transactions of "pharmaceuticals"[9]. In this regard, the present version of the French public health code ("Code de la Santé Publique") as amended in 2008[10] stipulates that for each incoming and outgoing transaction, the number and expiry date of all batches must be archived with the quantities supplied or received per batch.

The new legislative framework has hence a large impact on the whole supply chain from the manufacturer to the pharmacist level as the packaging chain and the IT system have to be adapted in order to encode and read Data Matrix data.

2. Technical Characteristics for Labeling and Printing

French health regulatory authorities have chosen to switch to Data Matrix labeling system because it is smaller and can contain a larger quantity of data[11] than the previous linear barcode.

The shape of the Data Matrix is either rectangular or square and its size depends on its number of rows and columns[12]. Each column and line of the Data Matrix is made of square or round symbols that can be dark (1 bit) or light (0 bit). Only specific sizes shall be used by manufacturers as the size determines the number of characters the Data Matrix can encode. The graphical structure[13] of the Data Matrix has the advantage that it enables omnidirectional scanning. The selection of the size and the form of the Data Matrix depends on the amount and the nature of the data to be encoded as well as on the space restrictions. Hence it can be advantageous to choose rectangular Data Matrix for outer-packaging that are longer vertically than horizontally.

The mandatory data contained in the Data Matrix system is the CIP 13 code, the batch-number and the expiry date[14]. The inclusion of the serial number is an option for manufacturers, especially for those producing costly products having a higher probability to be counterfeit. Its implementation was intended by the French health regulatory authorities as a measure aiming at tracing batches for health safety concerns. The inclusion of the serial number in the Data Matrix was thought to be too costly for pharmaceutical companies and to have delayed the implementation of the Data Matrix system. Batch-traceability will enable French health regulatory authorities to recall batches and hence secure the supply chain of medicinal products in France. In this regard, the implementation of the Data Matrix system leads in the same direction as the proposal made by the Strategic Council of Health Industries[15] ("Conseil Stratégique des Industries de santé", CSIS) on the 26th of October 2009 to commit pharmaceutical companies and wholesalers to guarantee the supply of the French market and identify cross-market exchanges.

Regarding the technical printing specifications, the French Medicines Agency requires the Data Matrix system to be printed directly on the outer-packaging and generally not on a sticker because it can easily be pulled off. Inkjet, laser or thermal transfer technology are allowed for printing[16]. To ensure print quality of the Data Matrix, technical printing specification should be observed and

[7] «Mise en œuvre de la traçabilité – Où en sont les acteurs de la chaîne de distribution?», X. Cornil, AFSSAPS, 09. 03. 10, available at *http://www.cipclub.org/institutionnel/fr/rencontres/pdf/R2010_Traçabilité_CORNIL.pdf.*

[8] See Point 4 of the notice.

[9] See definition in art. L5124 – 1 of the French public health code, referring to firms producing, importing or running a business with medicinal products, *http://www.legifrance.gouv.fr/affichCodeArticle.do?cidTexte=LEGITEXT000006072665&idArticle=LEGIARTI000006689973&dateTexte=&categorieLien=cid.*

[10] Amendment of art. R5124 – 58 of the French public health code by Decree n°2008 – 834 art. 2 of the 22. 08. 08, O.J. of 24. 08. 08, *http://www.legifrance.gouv.fr/affichCodeArticle.do;jsessionid=18FEAB31556E4B61C9182979FBFEB5C4.tpdjo10v_3?idArticle=LEGIARTI000019378325dateTexte=20100321.*.

[11] See "Les Cahiers CIP-ACL" n° 1 November 2007 and n° 2 December 2008, available on the website of the Club Inter-Pharmaceutique, *http://www.cipclub.org/.*

[12] The one selected is the ECC 200 as defined by the ISO/CEI 16022:2006 whose upper right corner module is light. Square Data Matrixes can have the following size: 18*18, 20*20, 22*22, 24*24, 26*26 and 32*32. The number refers to the number of lines and columns. Rectangular one can have size 12*36, 16*36 or 16*48. Other sizes cannot be used because their capacity to encode in terms of numbers and characters is either too low or too high for the purpose.

[13] The structure of the Data Matrix is bounded by a straight dark line forming a "L" and a dotted "L" at the opposite site forming a quadrilateral.

[14] In order to determine the precise nature of the data encoded, each data has to be preceded by an Application Identifier ("AI"). The AI (01) is used for the product code, (17) for the expiry date and (10) for the batch-number. The AI (21) is used to recognize the serial number that is optional. To avoid confusion in the coding process, no parenthesis should be put. Parenthesis can just be used for plain text printing in order to facilitate reading. To indicate that the GS1 128 syntax is used, the data must be preceded by "FNC1". The AI (01) identifies the product code that contains 14 digits, meaning the CIP 13 code preceded by a 0. Expiry date is identified by the AI (17) and should be written in the following form: YYMMDD. If no day is defined, "00" should be written. The format of the date in plain text is different as it should be written: MMYYYY. For the batch-number, contrary to the date, its length is variable and can consist of only numerical characters or of a combination of numerical and alphabetical characters. It is, advised not to select "0" as the first character of the batch-number to avoid any confusion. The batch-number in the Data Matrix system should be exactly the same as the one written in plain text. Because of its variable size, it is advised to place it at the end. Hence the data will look like: FNC101CIP1317YYMMDD10batch-number. Examples can be found on the website of the Club Inter-Pharmaceutique, *http://www.cipclub.org/.*

[15] The CSIS was created in 2004. While bringing together government officials and leaders of Health industries, it aims at making France more attractive for investment through concrete measures (*http://www.leem.org/medicament/conseil-strategique-des-industries-de-sante-537.htm*).

[16] Further specific printing provisions can be found on the website of the Association for automatic Identification and Mobility, AIM, *www.aimglobal.org.*

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checks should be carried out to guarantee its capture by scanning.

Regarding the location of the Data Matrix, it should be printed on one side of the secondary packaging and if possible on a flat surface near the "vignette"[17] in order to facilitate scanning at the dispensing point. In this regard, rectangular data matrixes are recommended for rounded packaging surface. For central marketing authorizations, the Data Matrix may be displayed in accordance with the EMA[18] outside the blue-box for space reasons. The CIP 13 code however remains printed within the blue-box.

Information in plain text[19] (batch number, expiry-date and CIP 13 code) should be printed on the same side of the outer-packaging of the Data Matrix system. However, this mandatory information can be displayed on another side of the outer-packaging depending on the size of the packaging[20].

3. Timelines for Implementation

Regarding the practical implementation of the measure, a transitory period from January 2008 until the 31st of December 2010 has been granted to give pharmaceutical companies the time to adapt their production lines[21]. During this period, specific provisions were provided depending on whether the marketing authorization was granted before or after the 1st of January 2009[22]. The notice provides that medicinal products being released on the market before the 1st of January 2009 with the old CIP 7 code can be sold until their expiry date.

Specific provisions have been provided by the AFSSAPS[23] for solutions for parenteral use and for medicinal products without packaging. In case of products for parenteral use (sold in plastic bags or glass bottles ≥ 50 ml), it is mandatory that the primary packaging contains the CIP 13 code with batch-number and expiry date and the outer-packaging the CIP 13 code and the Data Matrix printed on the label of the medicinal product.

Regarding medicinal products without outer-packaging a label with the CIP 13 code and Data Matrix should be glued on the product, indelible ink should be used and visible marks should appear in case of the label being pulled off. The batch-number and expiry date have to be written in plain text as well. On specific questions transitory arrangements are currently discussed which could apply until maximum the end of 2012.

4. Reimbursement Issues

As the capacity of the Data Matrix system in terms of data content is greater than the one of the linear barcode, one key issue for French health regulatory authorities and manufacturers is what type of data on the medicinal product is to be included in the Data Matrix. Data on the reimbursement status of the medicinal product and its serial number are currently not included in the mandatory data of the Data Matrix code.

Indeed in France, information about the price and the reimbursement status is included in the vignette whose future is unclear yet as no text provides explanation on its use after the 31st of December 2012[24]. In this regard, its abolition and the inclusion of the respective data into the Data Matrix labeling system would enable French health regulatory authorities to proceed to real-time prices adjustment.

5. EU Anti-counterfeiting Measures

Counterfeiting of medicinal products is a global problem and currently

[17] The vignette is the label used by French health regulatory authorities to give all economic and reimbursement information on the product. See Arrêté from the 07. 12. 2010, *http://www.legifrance.gouv.fr/affichTexte.do;jsessionid=90B495933315B7DCF13-D9908856146E8.tpdjo04v_2?cidTexte=LEGITEXT000005620472&dateTexte=20121231#.*

[18] See "Séminaire IFIS, suivi réglementaire articulation entre EMEA et Afssaps, Industriels et Afssaps", Afssaps, Mélanie Cailleret-France Roussel, DEMEB-DARP, 29. 06. 09, *http://www.afssaps.fr/var/afssaps_site/storage/original/application/16481d5030f3a49c3f8c4f506e8cfca6.pdf,* and EMA "Committee for medicinal products for human use, May 2009, Plenary meeting, Monthly report", 05. 06. 09, *.http://www.emea.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2009/10/WC500005831.pdf.*

[19] See art. R5121 – 138 of the French public health Code, *http://www.legifrance.gouv.fr/affichCodeArticle.do?cidTexte=LEGITEXT000006072665&idArticle=LEGIARTI000006914889&dateTexte=&categorieLien=cid.*

[20] Batch-number should be written in the following form, "Lot", Expiry date "EXP." and marketing authorization number "Médicament Autorisé n°".

[21] See provisions in art. R5124 – 58 of the French public health code as amended by Decree n° 2008 – 834 art. 2 of the 22. 08. 08, O.J. of 24. 08. 08, *http://www.legifrance.gouv.fr/affichCodeArticle.do;jsessionid=18FEA-B31556E4B61C9182979FBFEB5C4.tpdjo10v_3?idArticle=LEGIARTI000019378325&cidTexte=-LEGITEXT000006072665&dateTexte=20100321.*

[22] For marketing authorizations granted before 1st of January 2009, packaging chains that are not equipped yet with Data Matrix shall print the CIP 7 code in plain text and barcode 39 (as before) and the CIP 7 code also in the vignette. For packaging chains which are already equipped with Data Matrix, direct switch to Data Matrix labeling system and CIP 13 code has to be implemented, meaning that the CIP 13 code should be written in plain text with Data Matrix marking integrating the CIP 13 code, the batch-number and the expiry date. The same schedule is to be applied for non-reimbursable products, which only differ by the fact that they do not have a vignette glued on their packaging. Regarding products having been granted a marketing authorization after the 1st of January 2009, and that were hence directly given a CIP 13 code, the Data Matrix system can be directly implemented if packaging chains are already equipped with Data Matrix. The same schedule as for reimbursable products is foreseen for non-reimbursable and packaging should include the barcode and the CIP 13 code in plain text before being equipped with the Data Matrix labeling system.

[23] «Mise en œuvre de la traçabilité – Où en sont les acteurs de la chaîne de distribution?», X. Cornil, AFSSAPS, 09. 03. 10, available at *http://www.cipclub.org/institutionnel/fr/rencontres/pdf/R2010_Traçabilité_CORNIL.pdf.*

[24] See Arrêté of 07. 12. 10, *http://textes.droit.org/JORF/2010/12/14/0289/0015/.*

four main initiatives exist[25]. The first one is the World Health Organization's International Medical Products Anti-Counterfeiting Taskforce (IMPACT) that was created in 2006 and consists in building networks between stakeholders among countries to fight counterfeiting of medicinal products at global level[26]. The second international initiative is the Anti-Counterfeiting Trade Agreement (ACTA) that focuses on enforcing international standards on IP rights to fight counterfeit products[27]. The third one is MEDICRIME which is led by the Council of Europe[28] and aims at promoting public health ensuring that counterfeiting is sanctioned under domestic law. The last initiative is the European Commission proposal on the prevention of falsified medicinal products entering the supply chain[29] which is part of the EU's Pharmaceutical Package[30]. The draft legislation has been adopted by the European Parliament's environment and public health committee (ENVI) on the 27th of April[31]. A first reading in the European Parliament's plenary is expected during autumn and adoption is foreseen for the end of the year 2010.

Thus, the French legislation and counterfeit prevention measures would have to be adopted accordingly if the EU legislation implements further obligations. The Commission proposal aims at ensuring transparency of the whole supply chain and goes beyond the French provisions in this regard. The proposed measures are:

- *Mandatory safety features for prescription medicines*

The measures contained in the Commission proposal provide for specific safety features (RFID/2D Barcodes) in order to ensure identification, authenticity and traceability of medicinal products. The proposal foresees several safety features. One safety feature could be a seal protecting the inner-packaging. Another safety feature would have to ensure authenticity of the product including a check which is likely to take place at the dispensing point and could be carried out by serialization.

It is foreseen in the Commission proposal to apply the safety features on the outer-packaging of prescription-only medicinal products on a risk-based approach[32]. Focus is set on the risk of falsification with regard to the price of medicinal products and past incidences. Regarding OTCs, an evaluation report should be made by the European Commission in 4 years after the adoption of the Directive to decide on their inclusion.

While the scope of the safety features and the risk-based approach are still heavily discussed, the Commission proposal provides that records of wholesalers must contain the batch number[33]. The inclusion of a serial number which was implemented in pilot projects in Sweden[34] and the issue of data security are still subject to discussions.

Serialization consists in allocating a serial number at item level which is printed on the outer-packaging of each medicinal product. By this approach, the package integrity should be guaranteed. Random numbers should be printed on the outer-packaging and included in the safety feature[35]. In this system, information could be stored in a central European data base that can be accessed by pharmacists before dispensing the medicinal product. However, whether the EU safety feature is implementing such a serialization is not decided yet.

In any case, it is very likely that the EU system will be based on a 2D-barcode like in France and not on an ePedigree[36]. Unlike serialization, the ePedigree aims at creating a full record (through Radiofrequency Identification Technology/RFID) containing all transactions surrounding the medicinal products from the manufacturer to the dispensing point.

- *Impact on parallel trade*

Due to the general repackaging ban the measures proposed by the Commission could have an impact on parallel traders who have to repack-

[25] See in this respect: "Global Anti-counterfeiting Measures", I. Schofield, RAJ Pharma, pp. 407–410, July 2010; Counterfeits and "Opportunities for MEDICRIME, challenges for IMPACT", A. Chalmers, RAJ Pharma, pp. 417–418, July 2010.

[26] See *http://www.who.int/impact/en/.*

[27] See *http://ec.europa.eu/trade/creating-opportunities/trade-topics/intellectual-property/anti-counterfeiting/.*

[28] See *http://www.coe.int/t/DGHL/StandardSetting/MediCrime/Default_en.asp.*

[29] Proposal for a directive of the European Parliament and of the Council amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of medicinal products which are falsified in relation to their identity, history or source (COM (2008) 668) of 10. 12. 2008.

[30] The Pharmaceutical Package is a series of legislative proposals made by the European Commission to contribute to the strengthening of the current legislation on medicinal products for human use. The first legislative proposal aims at ensuring that EU citizens have access to reliable information on medicines, the second legislative proposal at strengthening the European system for the safety monitoring of medicines (pharmacovigilance) and the third one at fighting counterfeit medicinal products *(http://ec.europa.eu/health/human-use/package_en.htm).*

[31] See Report "on the proposal for adirective of the European Parliament and of the Council amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of medicinal products which are falsified in relation to their identity, history or source" (COM (2008) 0668-C60513/2008 2008/0261 (COD)), Marisa Matias, 07. 05. 10, *http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+REPORT+A7-2010-0148+0+DOC+PDF+V0//EN&language=EN.*

[32] See new art. 54a IV of the Commission Proposal (COM (2008) 668).

[33] See art. 80 of the Commission Proposal (COM (2008) 668).

[34] "EFPIA publishes report on anti-counterfeiting pilot", RAJ Pharma, pp. 319–321, May 2010.

[35] "Serialisation: Has Judgment Day Arrived for Counterfeit Drugs?," V. Postill, RAJ Journal, July 2010.

[36] See FDA News Release, "FDA Announces New Initiative to Protect the U.S. Drug Supply Through the Use Of Radiofrequency Identification Technology", FDA, November 2004, available at *http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108372.htm.*

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age medicinal products. While repackaging is still permitted[37], it is unclear to what extent changes on the inner-packaging are still permitted or not[38]. Furthermore, safety features could only be replaced under strict conditions and supervision. It is also discussed in the European Parliament whether the new safety feature shall be equivalent to the old one with regards to identification, authenticity and inviolability of the external packaging.

- *Further measures regarding the distribution chain*

Regarding the distribution chain, the proposal strengthens inspections that shall become mandatory for wholesalers[39] whose records shall contain information about the purchase/sale of medicinal products[40]. It is also foreseen to extend the scope of the rules regulating wholesalers, to other actors in the distribution chain such as brokers and traders which are auctioning medicinal products without physically possessing them.

- *Measures regarding GMP/inspections*

Concerning active ingredients imported from third countries, inspections on the ground of suspected non-compliance shall be made possible. Although no general application of GMP for excipients is foreseen, some categories of excipients shall be identified on a risk-based approach and be submitted to specific manufacturing requirements[41].

- *Internet sales and counterfeit medicinal products*

While the Commission proposal aimed primarily to prevent only the entry of counterfeit medicinal products into the normal supply chain, the European Parliament addressed the growing concern of internet sales as source of counterfeit medicinal products. The Parliament has thus introduced amendments providing that internet pharmacies should require a special authorization by the competent authority. For this purpose, a EU logo is to be created to help the public to identify authorized internet pharmacies that would be listed in a European Central Database. Awareness among the general public shall be raised through information campaigns[42].

- *Costs of the measures*

The costs of the measures would have mainly to be borne by the manufacturers. Indeed, the cost of printing the serial number on the outer-packaging is estimated at 0.5 to 1.0 cent per pack for manufacturers[43]. All measures are adding up to a total amount of 6.8 to 11 Billion Euro depending on the type of safety feature used. The costs the wholesalers would have to bear are estimated to about 410 Mio. Euro. Around 157 Mio. Euro are estimated for pharmacies.

6. Outlook

With the recent shift from lifestyle pharmaceuticals to life-saving medicinal products being counterfeit, counterfeiting is an increasing phenomenon in all EU Member States. France has taken the first step to address the issue by implementing a Data Matrix labeling system and introducing at the same time batch-traceability starting on the 31st of December 2010. However, important questions remain concerning the handling of pricing and reimbursement data and the possible implementation of a product-based serialization.

To this extent the outcome of the discussions about the European Commission directive on the prevention of falsified medicinal products entering the supply chain has to be monitored closely. A more stringent approach and further safety features by the upcoming EU legislation are likely to be implemented and to be in effect from 2012 onwards. Pilot projects are discussed in some Member States and by the EDQM. The political and technical developments therefore have to be followed closely during the years 2010 and 2011. First lessons on the labeling, printing and further technical requirements of a 2D-barcode system can be learnt from the French market given the obligation to apply the system to all medicinal products starting from the 31st of December 2010.

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[37] See art. 54 a II of the Commission Proposal (COM (2008) 668). Technical specifications should be decided under the comitology regime (art. 290 TFEU) as set out in art. 54 a IV.
[38] See amendment 54 in the Matias Report.
[39] See art. 77 V of the Commission Proposal (COM (2008) 668) / amendment 79 of the Matias Report.
[40] See art. 80 e of the Commission Proposal (COM (2008) 668).
[41] See art. 46 f of the Commission Proposal (COM (2008) 668) / amendment 38 of the Matias Report.
[42] See new Title VII a: Internet Sales, (art. 85 c / amendment 94 ff. of the Matias Report).
[43] EFPIA publishes report on anti-counterfeiting pilot, RAJ Pharma, pp. 319–321, July 2010.