The role of traceability in the pharmaceutical safety supply chain

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Abstract—The aim of this work is to demonstrate the need to trace pharmaceutical products and ensure their safety in the face of difficulties to operate the entire logistics in a country with continental dimensions devoid of infrastructure compatible with the needs of businesses and customers. This paper described the current pharmaceutical market and its business model, contextualizing the safety issue of the transport, counterfeiting, robberies and roads long distances that make it difficult to have control on the safety of medicines. In this context, this paper proposes alternatives, starting with greater control over the traceability of medicines. Secure tracking efficiency for medicines is one of the initial steps for solving some of the problems mentioned in the text.

Keywords—Traceability of medicines; counterfeiting of medicines; Safety supply chain; deviations; theft of medicines.

I. INTRODUCTION

The product logistics developments led to the growing need to optimize the process and thereby deliver products in the shortest possible time in the markets. This result is sometimes hindered by a poor structure and devoid of the necessary safety.

Supply chain traceability assists in process control and, therefore, in the survey of metrics that provide data, which favor the quality of management and the product.

In this complex environment, the technologies are the tool with the possibility to assist companies, customers and Governments to control the process and to reduce the risks for patients.

Traceability, according to [1] Resolution RDC nr. 54/2013, is the set of procedures that allow to trace the history, application or location of medicines through information previously registered by unique identification system of products, service providers and users, to be applied in the control of any unit of medicine produced, released or sold on national territory.

II. DEFINITION OF SUPPLY CHAIN IN THE CONTEXT OF THE PHARMACEUTICAL INDUSTRY

The pharmaceutical sector is composed of three main links in its supply chain, which are: production, distribution and dispensation. These steps are linked by product movement between one and another.

For the purposes of this study, the supply chain starts in the step of production, where the industry transforms inputs into pharmaceuticals, as provided by government regulations and business strategies.

The industry is responsible for the research and development processes well as the manufacturing of the medicines. It has a number of obligations and must follow the standards of quality and safety in its processes. Among these obligations, it has to maintain enough records of manufacturing, control and distribution of medicines, in order to ensure product traceability.

The distributor is part of the chain, purchasing the products for resale and, according to the requests received, realizes its shipment to your customer. The distributor delivers the shipment to a carrier, which will take the product to the customer, or in other cases, itself provides such delivery.

The dispensation is the point where the medicines are intended for end users and can be, for example, pharmacies, drugstores, hospitals, health centers or medical clinics. The provisions of Law nr. 5.991/73, article 6, informs that the dispensation of medicines is exclusivity of pharmacy, drugstore and Health Unity and dispensary of medicines. In this same law, the definition of dispensation, says that is the act of providing to the consumer: drugs, medicines, medical devices, paid or not.

The carrier is responsible for carrying out the movement of medicines among the links in the supply chain. This step is very important to pay attention to the conditions of the movement. The temperature, for example, is a very important factor in maintaining the quality of the product and, therefore, of the properties which give it effectiveness.

The entire pharmaceutical chain is regulated and supervised by the National Agency of Sanitary Surveillance (ANVISA). ANVISA is the competent body to regulate and oversee the industry, established by the federal Government through the Law No. 9.782 from 01/26/1999. According to the article nr. 8, the Agency responsibilities, complied with the legislation in force, are to regulate, control and inspect the products and
services that involve risk to public health. Among other assignments, it sets rules and items to identify medicines label.

A. Research and development

The activities of the pharmaceutical industry are based in the sector of research and development (R & D), which seeks to identify substances (active ingredients) that may give rise to new medicines, either from synthesis or extraction processes of nature of the compound.

B. Production of pharmaceutical specialties

Production of pharmaceutical specialties is the production of medicines in a way that will be marketed and made available to patients, ready to be used. Medicines will be produced in their most varied forms, such as tablets (with or without coating), capsules, drops, syrups, suspensions, granular, injectables, etc.

C. Marketing and marketing of proprietary medicinal products

Marketing and marketing of proprietary medicinal products involves the entire commercial process for medicines, such as market studies, characterization of the consumer, distribution partnerships, development of marketing strategy, formatting of distribution channels, developing of the branding, strengthening the company or product brand, etc.

D. Possible Controls the supply chain of medicines

Appropriate controls of the medicine can be made through procedures and documents that ensure the quality of the process. Figure 1 presents a list of documents and procedures that aim to control each of the phases, either directly on the product, whether in the process. When these steps sequence are properly followed one have proper control over the process. Verification can point out the flaws and fix the problems. For example, when the documentation is not obeyed in its integrity, deviations are identified and eliminated

Fig. 1 – relevant Documents at every stage of pharmaceutical chain. As "Pharmaceutical finished products traceability" – Gilberto Rossi – Sindsusfarma, SP. Nov, 2011

Although deployed controls, documents and certifications, there may be weaknesses in the supply chain, identified by entry points where can penetrate the illicit market actors. In a workshop conducted in São Paulo - Brazil, Dr Thomas Zimmer, International Society for Pharmaceutical Engineering (ISPE) Vice President of European Operations, identified the following points as the most fragile of the supply chain: APIs, Excipients, packaging materials, third parties (repackers),
distribution, dispensation, and internet sales. The insertion of specific prevention and preventive mechanisms in these points will discourage the action and the penetration of illicit drug products in the pharmaceutical supply chain [2].

III. DEFINING THE PROBLEMS

Medicines have been the target of several illicit actions. Some of the main actions that affect the Brazilian pharmaceutical market are the theft, embezzlement and smuggling. These bad practices contribute heavily to insertion of the health risk to the patients.

On the other hand, for companies the risk can result in economic and financial loss, and high costs relative to the image and the brand of the product. Additionally, for Government they face taxes revenue subtraction and loss of credibility.

Intentional falsification occurs when products are produced with insufficient amount of active pharmaceutical ingredient (API) [3] [4]. These fakes are also known as substandard, meaning products containing asset amount below the regular or specifications containing no active ingredient.

Lots of products "substandard" contain defects of quality or do not comply with the Good Manufacturing Practices and Distribution [5].

Because of the technical difficulties to imitate or copy a pharmaceutical product, correctly and entirely, we can say the counterfeiting was more important than it currently is.

As a result of this technical difficulty, criminality focus in this field, instead of being production of fake medicine, is trucks thefts and deflections, which are much easier from the point of view of the product, but with much more risk from the point of view of criminal operation as a whole. Interest to notice that counterfeiting is more directly linked to high value-added products.

IV. TRACEABILITY

The main function of medicine traceability is to promote its recall from the market. This gathering aims to remove, from the pharmaceutical market, products suspected of causing health hazard due to defect or failure of quality, which would undermine its performance (quality, safety and efficacy) [6]. The recall is only possible if it is linked with a solid concept of traceability, making it possible to collect any unit of the pharmaceutical product in any pharmacy, clinic, distributor, hospital, health clinic or any other unit of dispensation of medicines, and bring it back to the industry.

In other words, traceability is the action that makes possible to identify the path followed by the product, from production to consumer. Internally, in the producer installations, it means making the reverse path of the documents involved in its manufacture. This route permits to identify the raw and packing materials used, process, operators who handled any of the products, as well the controls carried out. This information makes it possible to re-examine the process, the materials used and the final product collapsed, and, therefore, to identify causes of eventual problems.

In the year 2013, after the publication of ANVISA, Resolution RDC No. 54/2013, was presented the first definition of traceability for medicines in Brazil, that is, "Tracking of medicines: a collection of procedures that allow a company to trace the history, application or location of medicines through information previously registered by unique identification system of products, service providers and users, to be applied in the control of any unit of medicine manufactured, released or sold on national territory ".

A. History of medicine traceability in Brazil

The traceability of medicines has always been linked to the gathering of medicinal products, in the event of a failure or quality deviation that would compromise patient care, allowing their rapid return to the manufacturer and to eliminate the likely risk.

However, it did not happen so simply. It took major events to grow awareness before the deployment of the Good Manufacturing Practices (GMP) in the pharmaceutical industries. These occurrences accelerated the development of GMPs in the world.

The first publication mentioning gathering medicines was made by the Food and Drug Administration (FDA)-Federal Register, in 1963 [7], from where can be extracted the first notion of what would be later called traceability, which, as explained, is the need for records of distribution of medicines:

§ 133,109 Distribution records. Complete records must be kept for each shipment in a manner that will facilitate the gathering, misuse or destruction of the product, if necessary. Such records must be retained for at least 6 months after the date of shipment and must include the name and address of the recipient, the date and the quantity shipped and manufacturing dates, tracking numbers or markings identifying the medicine shipped. If the medicine is handled under the control of the manufacturer, for following shipment to the establishments other than where it was produced, the records highlighted in this section must be maintained in these establishments." [7]

This first standard on GMP points the need to keep records of product distribution as mechanisms to withdraw from the market products improper for consumption. This practice, although already known and adopted by professionals in the pharmaceutical industries, can still be improved by the agents that operate in the market.

Other GMP documents were published by the World Health Organization (WHO), as the texts of 1969 [8], 1975 [9], 1992 [10]. In Brazil, in 1982, appeared one of the first documents, the GMP Manual SNVS's medicine of the Ministry of Health, [11], which said in its item 17.4. "For the eventual removal of a medicinal product be quickly arranged, there must be a distribution system that allows easy identification of your destiny".

We can, from these documents, extract the main objectives and reasons to track a product: facilitate product recall by removing those with suspected market failures; allow the trace of the product throughout the chain from manufacturing until the dispensation; assist in maintaining the safety of the use of
medicines and contribute to reduce the entry of illicit products in the pharmaceutical chain.

V. TECHNOLOGIES

For the most illicit or illegal activities mentioned earlier, the primary and immediate solution is fighting against crime, via supervision and police performance. However, for several reasons, it's not what happens in practice. Among the reasons can be listed the lack of police equipment, the absence of specific technologies to combat crime, the lack of material and human resources, among others. This is a problem involving the economic and social sectors, and that demand joint actions of public authorities and private initiative. [12]

Thus, it is important to know the appropriate existing technologies and their various applications, to enable effective control over the goods transported. Among the many solutions available today, different mechanisms, active in various stages of the process, can be related.

The applications of a system to unique identify an object, to capture, storage and transmit data, gives better control over the supply chain, therefore to its safety. As examples, it allows a recall and to prevent fake medicines to run into the regular market (v.g. the system identifies and detects products from cargo theft [3]).

Having an electronic system, with exchange of electronic information, represents gain of quality, therefore, security (for example, it prevents human errors and crosses available information from different sources in a short time).

A. Available tracing technologies

Several technologies are available that allow the tracking of products. According to Portugal e Paulino [13], a number of technological solutions can be applied to the sector: the printing of 2D codes (like Datamatrix) on packages, the use of forensic inks packs, the cryptographic signature, the security seals, the RFID labels, the packaging with special materials, the laser surface or the combination of multiple technologies.

Linear barcodes (1D): has low density of information unavailable for Mass Serialization. Low cost, infrastructure available. Is the code printed on the product packaging we consume daily, like cookies, milk, beverages, etc. Most products contains a barcode to identify it.

The code GTIN (Global Trade Item Number/Global Trade Item Number) is an identifier for trade items developed and managed by GS1, formerly EAN/UCC. The GTINs, formerly called EAN codes, are assigned to any item (product or service) that may be priced, ordered, or invoiced at any point in the supply chain. [14]

Fig. 2 – Representative image of a linear GTIN barcode 13

Bi-dimensional barcode (2D): between the bi-dimensional models available, there is the Datamatrix, nowadays elected by the pharmaceutical market technology as part of the solution to several problems in the supply chain. It is available for bulk Serialization, has low cost, though some adaptation of infrastructure is needed.

Fig. 3 – Representative image of a datamatrix code

B. Difficulties of traceability

The use of the bi-dimensional barcode in the production, storage, shipping or receiving is considered advantageous to, between others, low cost (in relation with RFID tags), record of batch numbers and dates; record of the numbers of batches used; connection between the production batch number and the raw materials used, management of physical inputs of goods and shipments using the SSCC, managing separation and release of consignments, record of movement of merchandises, physical inventory, creation of logistical units, assignment and remarking of SSCC, tracking inventory movements, connecting the SSCC, lot number, product and destination of delivery, receive control through efficient coordination with boarding warnings, co-ordination of orders and deliveries, sending acknowledgments of receipt, entering data of the products in inventory records and transmission of information for efficient management of orders and invoices [14], [25].

The application of traceability is also useful in the hospital environment, to ensure the unit dose and protection of the patient. Barcode technology is also an important tool to ensure the traceability of medicines used in the hospital environment, enabling 100% traceability of medicines delivered by the dispensing pharmacy [15]. Important to notice that to some authors [16] the traceability of the medicinal product in hospital is only possible if it is registered to whom, when and by whom was administered the medicine.

Although there are dozens of advantages, the difficulties inherent in this process are not negligible, as for example, the necessary reorganization of the manufacturing and distribution processes and operating procedures, vital to restructure the medicine supply chain [17].

C. What happens in the world market

Some models of traceability in deployment or already deployed can serve as a benchmark for other countries, including Brazil, which can absorb best practices in implementation in each of them. Short description of these models is given below.

1) Argentina: The Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT) has published in May 2011 the Disposición 3683/2011-Report 5/31/2011: “Traceability system of medicines that companies must implement. This reaches companies that has legal interference in the supply chain of marketing, distribution and dispensation of medicinal
specialties included in marketing Authorization for Specialities”. The health authority of Argentina accepts the code GS1-128 and RFID for a transitional period, but preferably companies should adopt, in the future, the GS1 Datamatrix – 2D- barcode”.

2) Germany: In Germany the tracing system is being implemented by the industry itself. The secuPharma, according to the European Policy 2011/62/1 of 6/8/2011 mending the policy 2001/83/EC (regulation concerning products medicinal for human use), includes additional measures to ensure the protection against counterfeit medicines. Each package is marked with a Datamatrix barcode containing a number of an unique product associated with a serial number. This requires an extension of the German reimbursement system (PZN8) to the Pharmacy Product Number (PPN) or National Trade Item Number (NTIN). The Datamatrix code contains the PPN or the NTIN both of which are incorporated into the PZN8. [18], [19], [20].

3) China: In April 9, 2008 China’s State Food and Drug Administration (SFDA) reported that the serialization would be mandatory for 275 therapeutic classes of products from December 2011. In May of 2013 the list was extended from 307 to 502. The regulation requires all drugs sold in the Chinese market. The program was divided into phases:

   • Phase 1 – Serialize and track all class 1 substances (subsidiaries), as of October 2007. 
   • Phase 2 – Serialize blood products, vaccines and controlled substances class 2 and injectable medications since October 2008.
   • Phase 3 – Serialize and track all medicines.

4) Italy: In Italy the objective of traceability is the prevention of fraud in the system of reimbursement of medicines of the Italian Government, through the Servizio Sanitario Nazionale (SSN). On the Decree of July 15, 2004 [21], the Ministry of health establishes a central database to monitor the manufacture of medicines for the reimbursement system. The database is managed by the Italian Ministry of Health. The central database will join, via internet, all data concerning the supply of label (bollini), numbered.

5) France: The French Agency for Health Safety (AFSSAPS) decided to extend the product code CIP-7 for CIP-13. The CIP code is managed and delivered by the Club Inter Pharmaceutique (CIP) which includes manufacturers, distributors, agents, organizations representing drugstores, pharmacists from hospitals and healthcare experts technical French [22]. From 1/1/2011 Datamatrix is mandatory for all pharmaceutical products. The code should contain the batch number, the expiration date and the product number (CIP13).

6) Turkey: In Turkey The process of tracking medicines started in October 2007 as the initiative of the Turkish Ministry of Health. In August 2008 the tracking system had its first demonstration for the sector, where were presented the objectives of the project. By September 2009 was running the pilot project for testing the efficiency of the system and to prove the model. Already in January 2010 the system began to operate in its first phase [23].

7) USA: In the State of California, the discussions led to the postponement of the implementation of traceability for 2015.

VI. PROPOSAL

To control of the entire pharmaceutical supply chain, from the production step until the dispensation step, it is proposed to print a Datamatrix barcode in each unit of the product available for sale. These units, belonging to a batch, will be marked with a Datamatrix, which contains an individual and unique serial number that identifies that item.

The sequence insertion of codes in production lines can be given following, as descriptive by GS1 standards, Brazil [24]:

2D code printing on secondary packaging, barcode printing GS1-128 on secondary packaging, barcode printing GS1-128 on tertiary packaging and barcode printing GS1-128 on pallet.

By means of suitable equipment, the 2D code is printed on the secondary packaging of the medicinal product. Then, the checking the printing quality by cameras and capture the data containing in the barcode (batch number, serial number, expiration date and number of registration number of medicine) [1] and transfer to the database, unit by unit. Each movement of the product is registered in the database, stating its position and location.

VII. CONCLUSION

The application of bi-dimensional barcode, such as Datamatrix, can be very useful in the control of illegal activities in the logistics chain for medicines, contributing to reduce robberies, counterfeiting, fraud, smuggling and diversions.

Additionally, it collaborates with the maintenance of the integrity and authenticity of the product, since existing a strong commitment from all agents (industries, distributors and pharmacies) in adopting and, effectively, managing the system.

The use of 2D barcode will become an element of high reliability in the transit of goods, assisting on the transit control. Therefore, it is expected there will be reduction of deviations and crimes through the distribution and marketing of medicines.

On the other hand, the use of this application, points to the costs reduction in the control of stocks. Also, by quickly providing quality information, the systems benefits agility in decisions making.

In a nutshell, in medicine traceability, the use of bi-dimensional barcode technology will bring immediate benefits and will contribute, as one of the necessary elements, for the safety of the whole medicines supply chain.

REFERENCES

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