A Strategic Approach for Serialization Through Packaging Manufacturer Integration

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Abstract — **The introduction of serialization of prescription medicinal products for seamless traceability along the supply chain requires significant changes in the processes of pharmaceutical companies and packaging manufacturers. With the entry into force of the EU Anti-Counterfeiting Directive 2011/62/EU in February 2019, pharmaceutical companies and packaging service providers have integrated serialization into their processes with enormous effort and significant investments, but in completely different forms - depending on the level of automation and the complexity of the process requirements. The IT infrastructure was and is an extremely complex area in order to completely reconfigure existing IT systems. Especially in the current crisis and highly unstable economic situation, many pharmaceutical companies are critically analyzing their technological steps. The potential for optimizing security services, such as serializing pharmaceutical packaging, is increasingly becoming the focus of those responsible, which is close to a kind of "efficiency wave" in terms of implementing security functions. What's more: According to many pharmaceutical manufacturers, a large proportion of production lines have become significantly more susceptible to failure, with correspondingly costly consequences, including higher demands on service personnel.**

Index Terms—folding box, label, package, serialization, temper evidence, unique serial code

I. INTRODUCTION

Directive 2011/62/EU requires prescription medicinal products to fulfil certain safety criteria. These include the presence of a unique identifier in the form of a two-dimensional data matrix code and anti-counterfeiting measures (temper evidence) and must ensure that the authenticity of the product can be verified throughout the supply chain from the manufacturer to the final consumer. The serialization process is a combination of data generation, coding, labelling, identification, and traceability.

Directive 2011/62/EU requires that each package of medicinal products has a Unique Serial Code (USC) in combination with the Global Trade Item Number (GTIN), Lot Number (LOT), Expiry Date (EXP), and the name of the manufacturer. All information is encrypted into a 2D data matrix code which is then printed on the folding box. The encrypted information is stored both in the national database system of the country where the manufacturer is registered and in the so called EU central hub. The manufacturer is responsible for affixing the unique code on the packaging of the medicine. The tracking of serial numbers is done in the supply chain and pharmacies check at the time of dispensing to the end user whether the code is recorded in the national database. If the code is not present in the system, or an error signal is received, the medicinal product will not be dispensed.

II. SERIALIZATION OF MEDICAL PRODUCTS

Serialization usually refers to the identification of each medicinal product to be serialised with a unique identifier in the form of a two-dimensional barcode on the packaging, as well as with an anti-tamper evidence (tamper evidence).

According to the legal provisions, marketing authorization holders (MAH) have the primary responsibility, i.e. they must ensure that all actors in the supply chain comply with the legal requirements under the Medicinal Products for Human Use Act (MPAH), the EU Regulation and the EU Directive. The MAH and pharmaceutical manufacturers have to ensure correct serialization, i.e. each product or each individual pack must contain the above-mentioned individual identification mark in the form of a two-dimensional data matrix barcode as well as an anti-tampering device. In many cases, the MAH and the manufacturer are identical. Ultimately, the MAH and more precisely the Qualified Person (QP) responsible must upload the serialized product data to the European Hub. According to Article 51(1) (2) of Directive 2001/83/EC, the QP ensures for medicinal products manufactured within the Member State concerned "that each batch of medicinal products has been manufactured and checked in accordance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization" [1].

According to Annex 16 of the EU guidelines on good manufacturing practice for medicinal products for human and veterinary use (*EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use; Annex 16: „Certification by a Qualified Person and Batch Release*"), the process of marketing or distribution of medicinal products comprises several stages: verification of the manufacturing process and analysis of the batch in accordance with the defined release procedures; certification of the batch by the qualified person (QP) in accordance with GMP and the requirements of the marketing authorization; and transfer of the released batch to the available stock intended for sale and/or export, taking into account the certification carried out by the QP. If the transfer of the exempted batch takes place at a location other than where the certification takes place, then this must be documented in a written agreement between the entities [2].

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The MAH remains responsible for the serialized product until it is sold or becomes the property of a GDP certified wholesaler. The wholesalers in turn must verify that the manufacturer has a valid manufacturing license, respectively that the parallel importers/distributors from whom they have obtained the medicine are GDP certified. This is not just a question of tracking medicines (Track-&-Trace).

Serialization is essentially based on the verification and comparison of serial numbers registered in national registry systems (NSRS). In practice, the marketing authorization holder should be able to provide information on the status of its serialized products at any time upon request by the authorities until the point at which responsibility is transferred to wholesalers. The same applies to wholesalers up to the point at which they transfer responsibility to pharmacies.

State institutions monitor compliance with legal provisions by conducting periodic on-site inspections of both drug manufacturers and wholesalers and/or parallel distributors. Inspections may be either pre-announced or unannounced. In order to be able to carry out a meaningful inspection, the responsible authorities must be linked to national registry systems. All currently active serial numbers, sample serial numbers and damaged or destroyed medicinal products are stored in the registers. In order to make the entire history of a serial number as transparent as possible, it shall be kept for at least one year after the expiry date or five years after the packaging has been put up for sale or distribution in accordance with Article 51(3) of Directive 2001/83/EC. In case of suspicion of falsification, the competent national authorities shall have the possibility to carry out an immediate check [3]. The sale of falsified medicines is almost impossible as each pharmacy checks the unique identifier of all serialized packages with pan-European standardized reading devices before they are made available to the patient.

Each Member State shall establish its own National Medicines Verification Organization, which shall implement a cross-border functional system of mandatory verification throughout the medicines supply chain. Each national organization is in turn linked to the European Hub. In Bulgaria, the five organizations that represent stakeholders involved in the production and distribution of medicines - the Bulgarian Generic Pharmaceutical Association, the Bulgarian Association of Wholesalers of Medicines, the Bulgarian Association for the Development of Parallel Trade in Medicines, the Association of Research Pharmaceutical Manufacturers in Bulgaria, and the Bulgarian Pharmaceutical Union - established the Bulgarian Medicines Verification Organization (BGMVO) on 14 March 2016 in Sofia. It was established as a non-profit association to support the implementation of Directive 2011/62/EU in Bulgaria. The main objective of BGMVO is to ensure the supply of patients with authentic medicinal products by building, operating and maintaining an effective system for the verification of medicines in the Republic of Bulgaria. In this direction, BGMVO works in close cooperation with both the state institutions in the field of health care and the European Organization for the Verification of Medicines (EMVO) [4]. The industry organizations of Bulgarian companies manufacturing and marketing medicinal products actively support their members in the analysis and evaluation of different strategies to meet regulatory requirements [5].

III. SERIALIZATION OF MEDICINAL PRODUCTS BY PACKAGING MANUFACTURER

With the implementation of Directive 2011/62/EU, some manufacturers of packaging and labels have started to offer a new service to the manufacturers and distributors of medicinal products: serialization of folding boxes (pre-glued) and open preforms that meet all legal requirements in the respective target market. In this way, they actively enter the serialization process and can become an integral part of an enterprise's solution. For this purpose, they must be able to fulfil some basic market requirements such as printing country-specific coding including a matrix with 2D data and plain text; the ability to apply different types of labels (bolines, vignettes, etc.); processing and exchange of serial numbers; highest print quality and legibility of serialization data, guaranteed by the use of advanced technologies such as OMEGA DoD UV inkjet printheads and visual control through high precision cameras [6]. The involvement of a packaging manufacturer can reduce the investment costs of the enterprise, as serialized packaging can be easily integrated into existing production processes.

To be able to engage in the serialization process, packaging manufacturers need to integrate an IT customer interface into their production process. In this way, generated serial numbers as well as other necessary product information can be transmitted directly to the packaging production line. In this way, each primary package is printed with a unique identifier in the form of a two-dimensional barcode, after which tamper-resistant devices (e.g. labels) are applied. In order to be able to exchange serial numbers, packaging manufacturers need to be registered in both the relevant national system and the European Verification System for Medicinal Products (EVMS). In addition, they have to prove the existence of a validated IT interface for information exchange certified according to Good Automated Manufacturing Practice (GAMP).

The application of anti-counterfeiting agents to each package makes reading the package insert virtually impossible without disturbing the originality of the package. That's why packaging manufacturer August Faller developed a combination label - the Tamper Evident and Multipage Label - that combines an anti-tamper agent and a multi-sided adhesive label leaflet. The integrated leaflet label is applied to the wide side of the box and is connected to a special flap, ensuring the box is tamper-evident. This flap is perforated and glued onto the retractable side lid of the folding box. The label is laminated using a high-precision two-stage perforator and allows the leaflet to be easily opened without damaging the tamper protection. For environmentally responsible companies, a laminate-free label made entirely of paper is also available, so that the packaging can be discarded with the wastepaper after use [7].

Thus, the combined anti-counterfeiting agent provides the most important information on the outside of a multi-page self-adhesive label compared to a plain leaflet. In this way, doctors, pharmacists and patients have quick access to the important information without opening the folding box and the original identifier remains intact.

This combined product brings with it great financial advantages for manufacturers: instead of a security label and a transparent hologram print, only the combined anti-counterfeiting agent can be applied. Any packaging machine that can apply conventional security labels on the box is also

able to put this product on the packaging. The requirement for a multi-page leaflet can be met by fully extending the surface of the multi-page self-adhesive label. The leaflet label can be extended to include up to 32 pages. The combined label is applicable to all standard folding box sizes and can be printed in 6/6 colors [8]. Once the serialization data is applied to the boxes, they are delivered to a customer who can immediately use them in the production process. The generated serial numbers (active, defective, unused) are forwarded via the interfaces to the ordering party, to the national medicine's verification organization and to the EVMS so that they are available for verification at any time.

In practice, there are different scenarios and possible solutions involving packaging manufacturers. One of them involves the integration of a packaging (folding box) manufacturer. In this case, the main objective of the use permit holder is to practically free itself from the coding of the packaging and to reduce the associated investment in purchasing printing devices for the packaging lines. At the same time, serialization does not substantially increase the number of folding box variants as each national market has its own language requirements anyway. In the EU, there are still no mandatory aggregation requirements and therefore the collection of such data can only take place after the packaging process has been completed or after palletization, as it is only at this stage that the physical link between the individual packaging components is made. Consequently, aggregation cannot take place at the packaging and box manufacturer. When serialization is implemented with the help of a packaging manufacturer, it is possible to reduce costs and, therefore, to realize small batches with specific requirements quickly and much more flexibly.

A second possible scenario is serializing the boxes before starting the packaging process. It has the advantage that the number of different box options that need to be sourced and processed by the manufacturer can be minimized. Thus, a dramatic reduction in packaging inventories can be achieved. Potential delays due to late orders and transport can be avoided. In addition, the design of small batches can be easily and quickly changed according to the needs of the pharmaceutical manufacturer, but for this purpose the know-how to apply inkjet printing must be available from the packaging manufacturer. In this respect, it is particularly important to underline that according to current EU regulations it is acceptable to serialize folding boxes off-line. Through subsequent late-stage customization (LSC), the boxes can be modified according to national requirements and incorporated into the production process without requiring modification of the packaging line [9]. Thus, good serial numbers can be sent to national serialization and verification systems and to the EU Hub. A single serialization device can seamlessly feed several packaging lines with serialized boxes, thus avoiding the installation of printing technology on each individual packaging line. This reduces the investment significantly and can be applied as a temporary solution in case of planned replacement or modernization of packaging lines.

A third possible scenario involves the serialization of already packaged medicinal products. In this case, market-neutral packaging is produced, i.e. without any national markings and trademarks. Only at a later stage are they branded using LSC, usually in dedicated logistics centers. In this way, it is possible to realize large production runs that exploit the available packaging lines efficiently.

In this way, multiple separate national variants of the same medicinal product are combined in a single production campaign, avoiding many short production runs and the associated frequent interruptions in the production process. The more labour-intensive the labelling and application of specific national markings, which could be done at a later stage by LSC, the more small batches could be linked into a single production process in case this is postponed until later. This scenario can only be applied in cases where the blister and leaflet are universal and do not contain specific national traits [10].

If the secondary packaging (folding box), the primary packaging (blister pack) has to be provided with specific (national) marks and signs, it is possible to personalize at a later stage by using flat folding boxes with subsequent packaging. In contrast to the previous scenario, here the blister can be 'inscribed' with a single two-dimensional code containing the product code, expiry date and batch number. In this way, labelling can be carried out reliably and without the risk of mistaken mixing of products from different batches. In this scenario, the packaging process is transferred to the logistics warehouse and almost always performed manually. This scenario is therefore only advisable for particularly valuable products or for small batch production.

Involving packaging manufacturers in the serialization process can reduce costs for pharmaceutical companies, as they will not have to purchase and install encoders and anti-counterfeiting machines. The exception to this is the simplest anti-counterfeiting option, where the side flaps of the box are glued so that opening the package results in its integrity being compromised. Pre-serialized packages can be used without restriction, with possible coding challenges (e.g. boxes too small, insufficient space for data application, lacquered surfaces) being passed on to the package manufacturer. At the same time, this is linked to the need for additional processes to exchange and control serialization data. The company must have information on the availability and status of the serial numbers generated at all times to avoid possible errors or misuse of the data. This in turn may require higher costs for IT architecture and/or staff training.

The inclusion of packaging manufacturers can never take over the function of a stand-alone serialization solution. It can only be implemented partially as an inextricably linked element of one of the other strategies. Interposing packaging manufacturers does not allow for a reduction of IT equipment costs on the part of the enterprise. In some cases, it may even lead to higher costs related to the need to create and manage new processes and exchange data between the participants in the serialization process. On the other hand, not all packaging manufacturers seek to actively participate in the serialization process, so it is realistic to assume that those that do successfully meet the technical requirements for this.

The main advantage of involving packaging manufacturers is to reduce the cost of equipment on packaging lines. With successful integration of packaging manufacturers, the need to install coding facilities such as laser printers as well as visual inspection and reject systems for defective packaging can be eliminated. Based on an average cost of €150,000 [11] for the above appliances and devices, it can be assumed that the total investment required to complete a packaging line can be reduced by nearly 30%. This would lead to a tangible

reduction in the financial burden, which mainly affects small and medium-sized enterprises.

The involvement of packaging manufacturers is only advisable for small and medium-sized enterprises when a well-functioning central repository of serialization data with multiple interfaces is in place, manned by highly qualified staff or external specialists. This requires a high degree of technological renewal and innovation activity in enterprises [12]. Packaging manufacturers can be particularly useful in small batch production. The use of pre-serialized packaging would significantly reduce the formatting time of packaging lines. This would allow especially small and medium-sized enterprises to respond flexibly to the requirements of different target markets.

IV. Conclusion

The implementation of the legal provisions for the serialization of medicinal products is a complex and capital-intensive process. The complexity of implementation and compliance is increased when the manufacturers of medicinal products fall into the category of small and medium-sized enterprises. They rarely have significant financial resources and find it difficult to establish the interdisciplinary teams needed to manage and control the serialization process. It is essential that the company holding the manufacturing authorization acquires a holistic view of the process and develops a serialization strategy that will allow it to reduce investment costs while allowing the use of know-how from external sources.

The strategic approach presented here can help accelerate the serialization process in small and medium-sized enterprises by outsourcing the coding activity. In this way, enterprises can significantly reduce equipment costs. On the other hand, it will increase the necessity to use universal interfaces for the exchange of serialization data between the participants in the process. Investment in IT equipment and specialists will increase. The focus will fall on defining, harmonizing and monitoring the serialization standards applied by the different actors.

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