1. Korrekturabzug /
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Serialisation: challenge and engine of change*),**)

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The implementation of the various regulations for serialising medicinal products and their traceability in the supply chain (Track & Trace), whether motivated by counterfeit-protection concerns or to prevent reimbursement fraud, presents large and small pharmaceutical companies alike with enormous technical, financial and organisational challenges. The absence of an industry-wide standard and the appropriate robust and proven hardware as well as software along with the great variance in requirements represent the greatest difficulties in developing an implementation concept and in routine operation. As a contract manufacturer, this situation is compounded by the many additional customer-specific requests. Here the pharmaceutical industry is breaking new ground in many respects. Serialisation also opens up absolutely new ways of questioning established modes of operation, of identifying potential improvements through more transparency and of raising efficiency and quality. It offers the opportunity to a pharmaceutical company to position itself as modern and future-oriented.

Introduction

With Directive 2011/62/EU published in mid-2011 to amend Directive 2001/83/EC, generally also known as the Falsified Medicines Directive (FMD), the European Union clearly demonstrated that it was intent on combating the growing problem of counterfeit medicines [1]. The core of the measures, as specified in greater detail in the Delegated Regulation (EU) 2016/161, was to be the identification of each individual sales package with an individual distinguishing feature or unique identifier (UI), consisting of a combination of product code and serial number. The UI was to be applied in human-readable text, but also machine-readable in the form of a 2D code (data matrix) [2].

The concept of serialisation, common practice in other industries for product protection, was already prescribed for medicinal products in Turkey at that time. In other countries, e.g. China, South Korea, USA or Brazil, comparable regulations were just about to enter into force or were in the process of being drawn up. So, it was foreseeable that a company in the pharmaceutical industry had to take this matter seriously and be well prepared so as to be in a position to continue being active on the global market.

Although the respective regulatory requirements, which have since become applicable, are all very similar, they still differ in not insignificant details. In Europe, in principle only prescription drugs and certain over-the-counter ones are subject to mandatory serialisation, whereby this distinction is not made in other regulations. In addition to the UI, there also continues to be a second security feature in Europe, namely an anti-tampering device (ATD), which has

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yet to be demanded elsewhere. China uses a 1D code and serial numbers provided by a public authority, in which the product number is integrated. Complete and continuous traceability across the entire supply chain will ultimately be demanded in the USA and Brazil (Track & Trace, T&T), which makes aggregation inevitable, i.e. the assignment of the UI of the sales package to the likewise unique identification number of the superordinate packaging level (parent-child relationship). In Europe, however, only "flat" serialisation is currently demanded, without aggregation, and the authenticity of a sales package is not checked against a central database, but rather by means of end-to-end verification [3]. Even though the FMD was conceived as the unified standard for 32 countries, there are many decisive national specifics to be considered in its implementation. The final question always remains as to the design of the serial number, the "serial number profile": How many digits may or must it have; is it of a purely numeric or alphanumeric structure; may it also include lower case letters; are there characters excluded from use; does it contain a fixed component, and if so at what position; does it have to be randomised?

Looking at this matter in detail, it soon becomes apparent that a number of challenges have to be overcome in order to successfully implement the requirements, and that pharmaceutical serialisation entails far more than simply imprinting a serial number and a machine-readable code onto a sales package – a classical iceberg phenomenon [4, 5]. Serialisation has an influence on almost all established processes and systems within a company and necessitates adaptation of all workflows. It is a very multifaceted and highly interdisciplinary area with many internal, but also external interfaces. After all, successful implementation of the requirements is not an option, but is in fact business-critical and a legal obligation.

Serialisation – a tremendous regulatory, technical and organisational challenge

It is found that serialisation is technically complex and conceptionally demanding to an equal degree for large, globally-operating marketing authorisation holders (MAHs) as well as contract manufacturing organisations (CMOs). While special solutions were initially possible for individual markets, e.g. China or Saudi Arabia, by retrofitting the packaging line, now holistic concepts are indispensable, whose quintessence is the complete integration of a company's packaging lines in the system topography and serialisation in the process topography.

Maybe the biggest challenge is in developing safe, simple, sustainable and expandable implementation concepts for a multitude of different regulatory requirements and deadlines, while coping with a lack of experience, proven technology and practicable established standards [6–8]. A fundamental deficit in almost all regulations with regard to such a complex and demanding task is the excessive room for interpretation and the absence of precise specifications for technical implementation. Furthermore, new requirements are constantly being added or existing ones modified. Developing and realising serialisation concepts is like shooting at a fast-moving target.

From the perspective of a CMO, the whole area becomes even more complex in that the customer's demands may differ widely in their scope and nature in technical, systemic, procedural and commercial terms. This comes on top of the regulatory requirements. On the customer side, there are often unclear or fragmented competences as well as changing contact persons or none at all. Moreover, CMOs and MAHs have their own oftentimes differing priorities, implementation plans, ideas and possibilities. There are new information channels, responsibilities and dependences between the CMO and MAH that have to be regulated. Finally, for the MAH there is often no understanding for the CMO's effort, costs or restrictions. In fact, serialisation can only work if the MAH and CMO are open-minded, constructive, cooperative and work together on eye level.

From the technical point of view, serialisation necessitates vertical integration of various systems on different technical levels. Large volumes of data are generated, which have to be administrated and archived (big data management). Today, data integrity has to be ensured not only locally, but also across the entire process and supply chain. Although countless providers of hardware and software have since appeared, initially it was not possible to rely on companies with the appropriate experience in this field. Therefore, in the early days it was effectively impossible to purchase fully functional installations and systems "off the shelf". All providers in this market segment, the big and small ones, the old and new, have to go through an appreciable learning curve which is yet to be completed today. Serialisation causes different, hitherto separate worlds to collide: Suddenly the mechanical engineer has to get involved with information technology and software, and a programmer has to develop an understanding of mechanics and production processes. In the absence of a technical standard, which, true to the Plug & Play principle, functionally integrates packaging lines and IT systems from different providers without proprietary interfaces and without huge implementation costs (Plug & Produce), the watchword has to be: *Keep it simple!*

Organisationally, serialisation requires an implementation team that

unifies a solid understanding of processes and technology from all areas and across all technical levels. Until now, many CMOs had little prior experience and expertise with regard to such multifaceted and complex matters. Additionally, implementation often had to be mastered with limited human resources, while having to synchronise implementation and ongoing operation. Workplaces and job profiles are changing in pharmaceutical packaging. The demands placed on staff qualification in the secondary packaging of medicinal products, where unskilled and temporary staff often used to be encountered, are increasing considerably. Entirely new competencies have to be established in the short term and assured over the long term. After all, the biggest challenge is to create awareness and understanding among all employees for the importance and implications of serialisation and to translate the modified working methods into routine procedures in a permanent and reliable manner.

Minimisation of complexity through standardisation

CMOs often have a broad spectrum of diverse customers with manifold profiles and possibilities – from the global corporation down to the distribution company with a handful of employees. They frequently use diverse packaging technologies and manufacture a large number of different products and forms of presentation (product diversity). Contrary to the situation for MAHs and originators, manufacture is not in series and to stock, but is order-related instead. It is rather rare for a packaging line to be dedicated to one customer or one product. Order fragmentation is high, batches often tend to be small.

In order to be prepared for serialisation in good time, CMOs were well advised not only to know, constantly monitor and consistently implement the regulatory requirements as part of a sustainable overall concept, but also to anticipate and consider customer requirements, even if the customer had yet to formulate them. Considerable investment also had to be made given unclear regulatory requirements, in ignorance of special customer requirements and without commercial agreements with the customer – a not insubstantial risk and a feat for companies, especially SMEs.

One principle for coping better with this situation is to minimise complexity through standardisation. Keeping one's own immediate, controllable complexity as low as possible is all the more important, as no industry-wide standard exists. Specifically, this means identifying the conceivable application scenarios, formulating the process requirements, defining the processes as simply as possible, while designing the necessary hardware to be as unified as possible. The result of such considerations could look like this:

- Obtain all devices used for serialisation from one provider, ideally always the same model (avoidance of interfaces, interchangeability).
- Fully equip all packaging lines for serialisation and aggregation (redundancy, sustainability).
- Offer only one type of ATD.
- Define meaningful trigger points for exchanging serialisation messages for each process.
- The most reliable and simplest process is defined as the standard and preferentially implemented.

As this principle is pursued by the CMO and MAH alike, this results in very diverse perceptions of these standardisation efforts for the two roles (fig. 1).

In the following, some aspects of the EU serialisation that repeatedly lead to misunderstandings and discussions are examined.

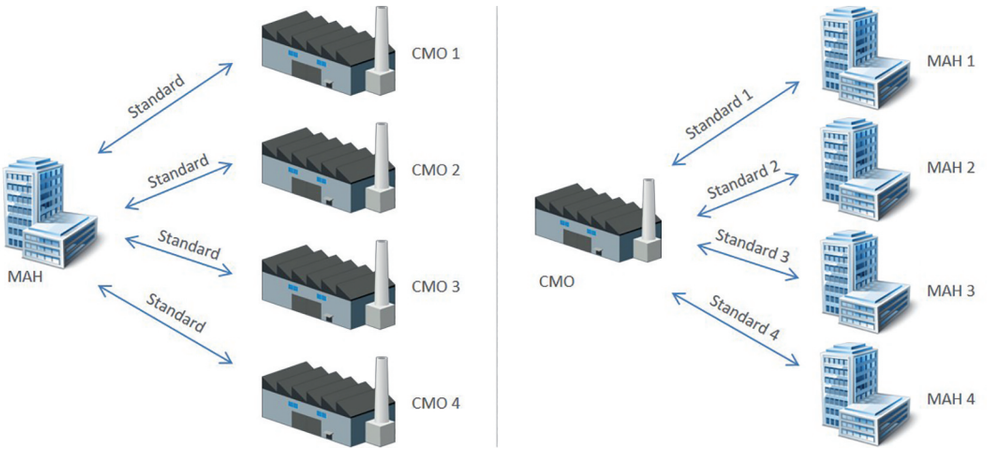
Serial number generation

According to EU regulations, the MAH bears responsibility that the serial numbers used satisfy the regulatory requirements with regard to structure, uniqueness and randomisation. This responsibility is consistent and plausible, as the MAH is also responsible for reporting the serial numbers to the EU hub or the respective national verification system, as well as for updating the entries there. But it is not a regulatory requirement that the serial numbers also always have to be generated by the MAH and made available to the CMO. Interestingly, this is the perception held by many MAHs, however. In fact, there are system providers that refer to the ostensibly greater security and actively discourage their MAH customers from having the CMO generate serial numbers, which is also possible.

Assuming a suitable and validated system for generating and administrating serial numbers, delegating this task to the CMO is objectively by no means more fraught with risk. On the contrary, the MAH and CMO elegantly dispense with a series of challenges that arise from the MAH providing serial numbers:

- The exchange of messages is reduced to an absolute minimum. The messages for requesting, transmitting and possibly receiving the serial numbers are eliminated. This reduces the implementation burden and the susceptibility to errors in ongoing operation and raises data security.
- Serial number reconciliation for numbers provided by the MAH is eliminated. This sustainably simplifies the entire process and integration, as otherwise it has to be completely ensured that all serial numbers for samples, on retracting the machine, for rejects, or otherwise for products not identified as compliant are recorded in the systems. One particular difficulty arises when the serial numbers for pre-printing folding boxes are used by an external supplier. In this case, seamless recording of all rejected serial numbers is often not even possible. Without the necessity of serial number recon-

Figure 1



Standardisation from the point of view of the MAH (left) and the CMO (right; Source of all figures: the author/ Losan Pharma GmbH).

ciliation, the MAH always has a "clean" system and does have to worry about serial number relics ("residue").

- If the CMO reports the serial numbers for good products to the MAH – in regulatory terms the MAH only has to report good products intended for the market to the EU hub or national verification system – ideally on shipping the good product, the necessity to send "decommissioning messages" is also eliminated and the exchange of serial numbers can be restricted to a single message (fig. 2).

Aggregation

Although aggregation is not a regulatory requirement in the European Union, it makes absolute sense from a logistic and process-related perspective and offers advantages for both the CMO and the MAH. On the one hand, aggregation ensures that the physical product matches the system data 100 %; the often raised question of the maximum deviation allowed between the number of good products and the serial numbers identified as "good" does not arise. On the other hand, the possible traceability allows full transparency on the manufacture and path of sales packages, which may be helpful in the case of quality incidents or other matters. If a CMO offers aggregation to an MAH, the offer should be accepted because each system for generating and administrating serial numbers, after the appropriate configuration, is in a position to process aggregated data and yet report "flat" serialisation information to the EU Hub or the national verification system without aggregation trees.

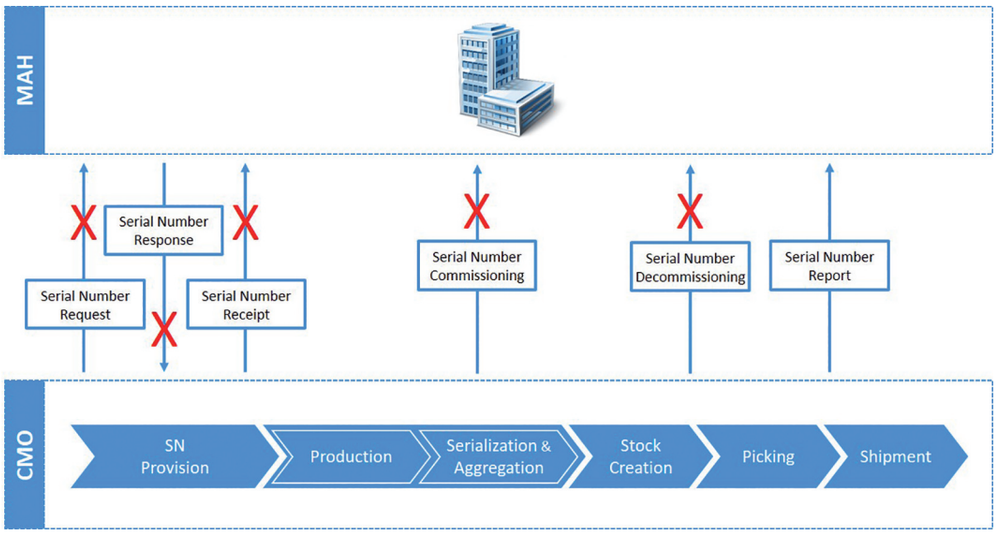
Master data management

Whereas the information hitherto exchanged between the MAH and CMO to conduct the business relationship was extremely simple and essentially limited to the approval dossier, the customer's product name and number as well as the order and information on packaging materials to be used, serialisation results in quite different and much more extensive requirements arising for master data exchange – or rather master data synchronisation – and the scope of the transaction data to be exchanged. Master data management will take on an even more prominent and production-relevant role in the future given the interaction of the many systems on different levels with manifold configuration options for the MAH as well as for the CMO. New, holistic and robust master data concepts are imperative for the functioning of internal processes. Nevertheless, the MAH also has to understand that the CMO will require more extensive and always up-to-date information in order to fulfil the task in the future. The high paper burden still widespread in the pharmaceutical industry has led to the relatively new phenomena of automated and proactive provision of master data, open and coordinated handling of it, and a common understanding for its importance, which are absolutely fundamental prerequisites for serialisation functioning in routine operation [9].

Validation

Large-scale serialisation cannot be mastered without a suitable system for the administration of serial numbers (T&T system) that integrates seamlessly in the company's IT topography dependent on the respective framework conditions. Meanwhile, a manageable group of credible system providers has emerged. Although their systems are func-

Figure 2



Possible message flow between MAH and CMO. In case of the CMO generating serial numbers, only one message has to be exchanged (serial number report).

tional and tested, there is a certain lack of maturity apparent, especially in interaction with competitor systems, which makes their implementation and use for entering production a demanding undertaking, despite optimal preparation. Updates and bug fixes are still common, unfortunately. Additionally, due to the absence of an industry-wide standard, every provider is more or less inclined to impress his distinctive stamp on the practice.

The T&T system, including its interfaces to other internal IT systems, has to be validated in accordance with established models, of course. This alone is insufficient in the light of the high and necessary configurability of the T&T system desired and the fact that internal and external parties, levels, applications, interfaces, device functionalities and other systems are involved and interact mutually. "Horizontal", isolated validation of the T&T system has to give way to a "vertical", holistic validation of the T&T domain (fig. 3). Care has to be taken that the differences and influencing variables are clearly identified in order to test them in the respective validation ("use case verification") that takes the entire T&T process into consideration. A modular approach is recommended to keep the validation workload as low as possible.

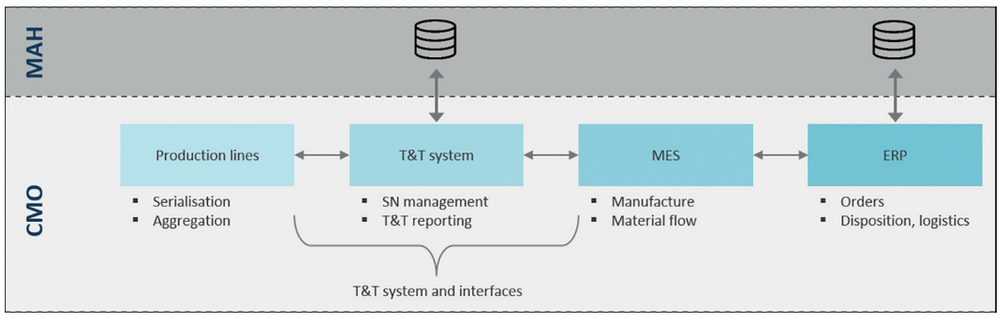
The necessity of validation is indeed undisputed and the need to safeguard serialisation is justifiably very pronounced among MAHs. However, surprisingly yet not infrequently, CMOs are met with a lack of understanding of their demand for each MAH to conduct use case verification at least once depending on the specifications – and in good time prior to the expiry of the deadline for implementation. Rather than being seen as a justified and useful measure for safeguarding serialisation, instead doubt in the validation status of the T&T system is often triggered.

Conclusion

Given the lack of unified standards for the entire pharmaceutical industry, the field of serialisation with all its regulatory facets presents a huge challenge. In order to adequately meet this challenge, MAHs and CMOs have to move closer together and cooperate in a spirit of partnership more than ever before. All players are breaking new ground: MAHs, CMOs, machine builders, software providers, but also auditors and inspectors. Conservative thought patterns and time-honoured procedures are no longer expedient and up-to-date. Courage to enter into open-ended and certainly controversial discussions as well as openness for alternative concepts are needed.

Moreover, all participants – associations, enterprises, providers – should work energetically, constructively, goal-oriented and beyond self-interests to overcome the lack of maturity of hardware and software that currently prevails, to make systems more robust and to work with a combined effort towards an industry-wide standard. Even though, regrettably, initiatives like OPEN-SCS could no longer be rendered tangible in good time, work must still continue unabated to this end. Because even once implementation has been performed successfully, there will come a time when a process has to be changed – due to a machine being exchanged, a system replaced, upgraded or as a re-

Figure 3



The T&T domain encompasses all levels, systems, internal and external interfaces and MAH-specific configurations involved in the T&T process.

sult of a change in regulatory requirements.

However, serialisation also offers opportunities and triggers an unprecedented situation of change. Driven by regulatory demands, the pharmaceutical industry, which tends to be innovatively inhibited and lagging behind other industries technologically often by years, is experiencing a technological push towards automation and digitalisation (Pharma 4.0) [10].

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