Dear Sir or Madam,

Today we would like to inform you about the following topics:

1 LEGAL BASIS

In July 2011, the amendment of Directive 2001/83/EC by Directive 2011/62/EU was introduced to prevent the entry of falsified medicinal products into the legal supply chain.

With publication of the delegated regulation (EU) 2016/161 on February 9th, 2016 the detailed rules for the safety features appearing on the packaging of medicinal products for human use were announced and implemented into national law. This regulation will come into force on February 9th, 2019 and has far-reaching consequences for the marketing authorization holders of medicinal products subject to mandatory verification, i.e. those medicinal products that must carry the safety features.

Within the regulation, the detailed rules for the implementation of the directive are laid down, among others:

- the technical specifications of the unique identifier (e.g., carrier, printing quality),
- the general provisions on the verification of the safety features (e.g., authenticity, decommissioning),
- the modalities of verification of the safety features and decommissioning of the unique identifier by manufacturers, wholesalers and by persons authorised or entitled to supply medicinal products to the public,
- the establishment, management and accessibility of the repository system (upload, EU hub, data protection, data ownership, access, etc.),
- the obligations of marketing authorization holders, parallel importers and parallel distributors (e.g., product recall, theft, free samples),
- the obligations of the national competent authorities and
- the lists of derogations (annexes I and II) and notifications to the commission.

As a general rule, all prescription-only medicinal products must bear the safety features. Exceptions are listed in annex I (“white list”) and II (“black list”): In annex I, the medicinal products are listed that are not allowed to bear the safety features (e.g., medicinal gases, homeopathic medicinal products), and in annex II those medicinal products are listed that must bear the safety features even

though they are not subject to prescription (at the moment, only omeprazole gastro-resistant hard capsules).

All other medicinal products must not bear the safety features.

The safety features are composed of:

- the unique identifier and
- an anti-tampering device.

1.1 Anti-tampering device

With the anti-tampering device, it can be verified whether a manipulation (e.g., opening) of the packaging of a medicinal product has taken place. In the regulation, there are almost no specifications given, however, in the Q & A on the subject of safety features for medicinal products by the EMA it is recommended to follow the CEN standard EN 16679:2014.

1.2 Unique identifier

By definition, the unique identifier means the safety feature enabling the verification of the authenticity and the identification of an individual pack of a medicinal product. The unique identifier consists of:

1. the product code
2. a serial number
3. the batch number
4. the expiry date and
5. a national reimbursement number, if not already integrated in the product code.

This information is to be printed in a two-dimensional barcode (data matrix code) on the outer packaging.

In this newsletter, we will not go into further detail on the composition of the product code, the detailed rules for the serial number and the data matrix coding.

In short, the serial numbers of the individual packages are uploaded to the national or the European verification system before the release for sale. These repository systems save and manage the numbers. Before individual packages are supplied to the public, the unique identifiers are scanned and authenticated in the national repository. It either reports the authenticity of the number (the medicinal product is then booked out of the system and can be handed out to the public) or the suspicion for falsification if the number is not available in the repository. Special cases such as packages for health care institutions, free samples and others are described in the regulation.

1.3 Data management

Every member state of the European Union as well as Liechtenstein, Switzerland, Norway and Iceland needs a national repository system that is organised by stakeholders and with which the data from the packages of the medicinal products is managed. The national systems are linked to the European hub which can be understood as a central information and data router within the community.

The member states have the possibility to either develop a system of their own or to use a blueprint: This is a sort of copy of an already existing system that is (co-)organized by the EMVO (European Medicines Verification Organisation, a consortium of several European associations).

So far, Germany is the only member state having made the decision to develop a system of its own. This national repository is developed by the organization securPharm e.V., a consortium of pharmaceutical, wholesaler and pharmacy associations (BAH, BPI, vfa, PHAGRO and ABDA). The operator of this national repository is the ACS PharmaProtect GmbH that has also been founded by the associations.

The European repository is managed by the EMVO which is also composed from several European associations.

So far, Germany and Sweden are the two member states that have made the greatest progress in creating the technical prerequisites for a functioning security system. In many EU member states, it has not yet been decided in which form a national repository is to be organized and how the technical prerequisites will be met.

2 RELEVANCE FOR PHARMACEUTICAL COMPANIES

Pharmaceutical companies that only manufacture medicinal products not subject to mandatory verification merely need to adapt their product information to the new QRD template (see section 3.2).

The other pharmaceutical companies should ideally already start now with the implementation of the regulation as this will take some time. The interaction of all company departments is complex and should not be underestimated. We can only point out a small portion of all necessary changes. It is also important to mention that the manufacturers of the hardware and the providers of the software, whose services are required for the implementation of the individualization of medicinal product packages, are already high in demand. Therefore, this can lead to longer waiting times for orders.

2.1 Conversion of the production line

In order to label each single package of a medicinal product with an individual serial number of its own, the corresponding technical provisions have to be installed on the production line, e.g. a printer and scanning devices for monitoring of print. The machines have to be acquired, need to be qualified according to the relevant guidelines and have to be installed.

2.2 IT for the creation of randomised serial numbers

In order to create and manage randomised, unique serial numbers in line with the requirements, an electronic system is necessary. This IT system must be integrated into the already existing systems and must also ensure the upload of the created and assigned serial numbers to the national repository or the European hub.

2.3 User contract with the providers

For the use of the national repository and of the EU hub, the pharmaceutical company needs to conclude a contract with the respective provider. In Germany, this is securPharm e.V. for the national repository.

If one wants to place medicinal products that are subject to mandatory verification on the market after February 9th, 2019, a contract with securPharm e.V. is inevitable. This also applies to pharmaceutical companies based in another member state who want to place nationally authorized medicinal products (not from a MRP/DCP) on the market.

If products from an MRP/DCP are to be placed on the market it is sensible to upload these directly via the EU hub. In this case, a contract with the EMVO is also necessary. It has however not been finally decided if a contract with the EMVO is necessary in any case.

The user fees charged by securPharm e.V. consist of:

- a one-off set-up fee (staggered: The later the conclusion of the contract, the higher the fee)
- a yearly service fee (progressive reduction: The more companies become members of securPharm e.V., the lower the service fee)
- a fee per data set or packaging volume (progressive reduction: The more packages are reported, the lower the fee per data set/packaging volume).

2.4 Agreement on the delimitation of responsibility with contract manufacturers

A contract manager may also notify the serial numbers to the national repository or the EU hub in the course of the production of individualized packages for medicinal products, however, he must be officially appointed to do so by the pharmaceutical entrepreneur. The pharmaceutical entrepreneur remains contract partner of securPharm e.V., the use and, if applicable, the upload of the serial numbers must be described in an agreement on the delimitation of responsibility. The pharmaceutical entrepreneur is always responsible for the upload of the data of his products to the repository system before placing the products on the market.

3 TO BE CONSIDERED FROM A REGULATORY POINT OF VIEW

From a regulatory point of view, the deadlines for implementation that are applicable for the placing on the market as well as for the update of the product information have to be considered.

3.1 Deadlines for implementation

After publication of the delegated regulation on February 9th, 2016, marketing authorisation holders of medicinal products subject to mandatory verification have 3 years to implement the new rules.

Medicinal products subject to mandatory verification that are released for sale by the QP from the 9th of February 2019 on must bear the safety features, otherwise, they may not be sold or distributed.

Medicinal products subject to mandatory verification that are released for sale by the QP before the 9th of February 2019 and were neither repackaged nor relabelled after release may be marketed, distributed and sold up to their expiry date.

This means that even for several years after the deadline comes into force, there might be medicinal products subject to mandatory verification available on the market that do not bear the safety features because they were released for sale before the deadline.

For three EU member states, there is a derogation: Belgium, Greece, and Italy may apply the regulation at the latest from the 9th of February 2025 on, with a delay of 6 years, as they had already implemented a system for the verification of medicinal products and for the identification of single packages at the time of coming into force of the regulation.

3.2 Update of all product information

At the same time as the regulation, a new QRD template for the product information has been published by the EMA. In this binding template, the sections 17 ("Unique identifier – 2D barcode") and 18 ("Unique identifier – human readable data") have been added to the labelling.

As the addition of these sections is a change of the labelling, this change is subject to a formal variation. However, the competent authorities have provided the pharmaceutical companies with an uncomplicated way of declaration:

The update to the new QRD template may be submitted with any regulatory action concerning the texts (i.e. all types of variations – IA, IB and II – as well as with renewals and similar applications). There is no classification or category of its own. However, if it is part of a type IA variation, no further changes of the QRD template may be performed.

The pharmaceutical entrepreneur is given a timeframe of three years for the implementation of the update which is the same as for the implementation of the safety features, until February 9th, 2019. By then, all texts should be updated.

If no suitable regulatory procedure is performed during this time, the QRD update has to be declared as a so called "non-variation" according to article 61, number 3 2001/83/EC (changes to an aspect of the labelling or the package leaflet, not connected with the summary of product characteristics; with costs).

An important note in this context is that the update to the current QRD template (addition of sections 17 and 18 to the labelling) does not mean that the safety features have in fact already been implemented with this variation (type IA) or will be added within a short time after the variation (type IB, II). Instead this is seen as a declaration of intent that the safety features will be implemented by February 9th, 2019.

It is also to be taken into consideration that an update of the product information must also be performed for those medicinal products that are not subject to mandatory verification. For these products, sections 17 and 18 are also added to the labelling, together with the note "not applicable".

For the deadline for the implementation of the text updates there is also an exception for Belgium, Greece, and Italy. The CMDh recommends that after the elapse of the three years, the member states should be contacted directly in order to receive information on the currently valid national deadline for the update.

4 SOURCES AND FURTHER LITERATURE

- Commission delegated Regulation (EU) 2016/161 of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use
- CEN standard EN 16679:2014 "Tamper verification features for medicinal product packaging"
- European Commission: Safety Features for Medicinal Products for Human Use, Questions and Answers, Version 5
- Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products
- securPharm: Joining forces for more safety in the pharmaceutical market, An overview of the provisions of the Delegated Regulation (EU) 2016/161 and the German system for authentication and verification of pharmaceuticals

- securPharm: Regeln zur Codierung verifizierungspflichtiger Arzneimittel im deutschen Markt ("Rules for the coding of pharmaceutical packages subject to mandatory verification in the German market", only available in German)
- securPharm: Status report 2016

Best regards

The DiaMed Team