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***New falsified medicinal products' distribution prevention regulation: legal
issues and good distribution practice for pharmaceutical companies***

BACHELOR THESIS

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DECLARATION OF HONOUR:

I declare that this thesis is my own work, and that all references to, or quotations from, the work of others are fully and correctly cited.

(Signed)

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SUMMARY

Starting from the late 2000s the validity of the medicinal products became one of the most important issues to be considered, as the level of falsified medicinal products sales significantly increased. In order to solve this issue, the Directive 2011/62 / EC (3) on falsified medicinal products for human use was introduced and now serves as a basis for the distribution of medicinal products, which only allows licensed pharmacies and approved retailers, including approved Internet service providers, to be included into the movement of the product. This directive introduced safety signs aimed at preventing the entry of falsified medicinal products into the supply chain of legal medicinal products (from the manufacturer to distributors, pharmacies and hospitals) and, consequently, to the patients. It is important that patients can recognize reliable sources and be aware of the risk of illegal sales. It is interesting to note that in the EU not only a two-dimensional code will be used to track individual packages of medicinal products, but also an unauthorized opening indicator, since in the absence of an indicator only the package is actually traced, but not its contents. Characteristically, the regulations harmoniously fit into both European and International regulation. In addition, the regulation prescribes encryption into a unique identifier of medicinal product the information described using a standardized international nomenclature, which will serve not only the objectives of traceability and protection against falsification, but also improve the collection of pharmaco-epidemiological and pharmacovigilance data. The new regulation contains other norms that allow a better understanding of the problems of traceability and their development in the EU. It is emphasized that all prescription medicinal products registered in the country and some non-prescription ones (right now only one - Omeprazol), must be labelled with a unique identifier by the manufacturer. The main idea of the traceability mechanism in the EU is the practice of "step back - step forward".

Consequently, the new regulation also introduced new obligations for wholesalers, which concern standards in the quality system, personnel training and hygiene, facilities and equipment, documentation, thus updating the Good Distribution Practice. Implementation of this system in Latvia required improvement in the IT infrastructure, which resulted in significant costs for manufacturers, distributors and pharmacy chains. Regulatory access to the database is also a separate aspect of the implementation of this project and had to be agreed at the initial stages.

Moreover, in the first month when the regulation came in force, the European Union IT infrastructure was detected as not ready to perform correctly with given number of transactions and users, therefore the distributors and producers faced a number of problems when the scanned data were not displayed or verified correctly. This cases are repeating almost every week, urging the distributors to move the packages to the quarantine area and not being able either to return, or to sell the medicinal products, even despite the fact that the medicinal products are not falsified, are approved by laboratory, and even in case of the reimbursed medicines or medicines for the hospitals, that are urgently needed for patients in critical conditions. Trying to solve these issues the companies are usually reported that the problem is on the data repository level and the companies have to quarantine the product until a problem is solved. This occurs also due to the challenge for the manufacturers to report on the volume of production of medicines in advance and buy the unique codes for each batch from the European hub, which is not always possible in the conditions of market volatility and demand for it. Disregarding the fact that this issue was unpleasant, it was mostly solved by the producers and distributors, who have predicted the possibility of the failure and hedged the

risks by ordering, producing and importing the medicinal products before the 09th of February, to secure availability of necessary medicinal products on stock for one or two months ahead, until the IT issues would be solved. However, the drop in sales was already noted, as while the producers were trying to comply with the requirement they were not able to move the goods in a regular amount, therefore the financial ratios also dropped.

Accordingly, a number of problematic situations in connection with the patient's rights arise because of the quarantined medicines: first, medicinal products for patients from the reimbursement list are not available in a timely manner, though similar ones are available, but for money; secondly, medicinal products for hospitals, prisons and other social and state institutions responsible for treating the population are not available in a timely manner; thirdly, medicinal products, which should be delivered in time according to the public procurement contracts are also not available. In a given situation, a violation of a number of patients' rights occurs, as well as a conflict of interests and restriction of the distributor's freedom. Violations of patient's rights or lack of attention to them can have serious health consequences. Such type of a hidden discrimination in healthcare is a powerful barrier to access the health services and affects their quality.

Summing up, given the positive impact of the new regulation for the patients' and the overall situation, this regulation put the producers and distributors under additional pressure they have to deal with and also may negatively affect the patient's rights.

TABLE OF CONTENTS

SUMMARY	2
TABLE OF CONTENTS	4
INTRODUCTION	5
1. EUROPEAN UNION PREVENTION REGULATION OF THE ENTRY INTO THE LEGAL SUPPLY CHAIN OF FALSIFIED MEDICINAL PRODUCTS	8
1.1. Problem of the falsification of medicinal products for human use.....	8
1.2. Background of the regulation aimed at prevention of distribution of the European Union 10	
1.3. Updated directive and delegated regulation of the European Union	12
2. GOOD DISTRIBUTION PRACTICE FOR PHARMACEUTICAL COMPANIES: ORIGINS AND AIMS ...	15
2.1. Current situation on the GDP in the pharmaceutical industry	15
2.2. Updated duties of the pharmaceutical companies.....	16
3. CASE ANALYSIS OF THE DISTRIBUTOR IN LATVIA	18
4. POSSIBLE CONFLICTS AND PROBLEMS DURING THE IMPLEMENTATION OF THE NEW FALSIFIED MEDICINAL PRODUCTS' DISTRIBUTION PREVENTION REGULATION	21
4.1. Challenges pharmaceutical companies and another distributors face.....	21
4.2. Legal conflicts.....	22
CONCLUSIONS	28
BIBLIOGRAPHY	31

INTRODUCTION

After the 2010 the European institutions have been widely reporting an alarming increase in the number of medicinal products containing poor quality ingredients or counterfeit ingredients that do not contain active ingredients or contain them in the wrong dosage (too high or too low), considering this a threat to the patient health as such and also the public health issue. These types of the medicinal products were widely concerned as falsified or counterfeit and create a risk, that the disease with this product will not be treated or the adverse outcome and severe side effect will occur. Moreover, the interaction with this medicine with other medicinal products or medicinal devices that patient is using on a regular basis is unpredictable and can endanger the life and health. This is due to the fact the falsified medicine usually is not controlled or regulated by the safety or quality standards, that are presented by the regulatory authority of the country in compliance with the EU registration procedures¹.

It is suggested that patients should be aware of the risks, that might be created by the illegal sales and usage of the falsified medicinal products and support the relationships between the producers and patient, protecting all of them via creating the binding legislation on this point. Consequently, the Directive 2011/62 / EC (3) ²on falsified medicinal products for medical use was created in the way to serve as a basis for the distribution of medicinal products. The new legislation created a path that allowed a limited number of representatives of industry (e.g. only licensed pharmacies) to be included into the medicinal products' supply chain. It is important, that the new legislative framework introduced safety signs aimed at preventing the entry of falsified medicinal products into the supply chain of legal medicinal products (from the manufacturer to distributors, pharmacies and hospitals) and, consequently, to the patients. Patient rights' protection organizations in connection with other institution have to raise awareness by informing patients and increasing the safety of medicinal products³.

Still, during the implementation of the new regular framework, a big pressure was putted on the retailers and other institutions. The essence of this innovation lies in the fact that the unique number of each pack will allow one to track and identify medicinal products in real time throughout the entire chain of medicinal products: manufacturer - distributor - pharmacy or hospital. The last phase of the Directive came into force on February 9, 2019. From this point on, prescription medicinal products that are sold in the EU must have a serial number, a two-dimensional code and protection from the first opening. All products that were approved for sale before February 9, 2019, may be in circulation before the expiration date or before the patient purchases it (whichever comes first). Manufacturers will enter the information contained in a unique identifier for each individual medicine in the EU central database, that

¹ European Commission. New safety features for medicines sold in the EU - Questions & Answers, Available on http://europa.eu/rapid/press-release_MEMO-19-802_en.htm. Accessed June 04, 2019.

² 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 Text with EEA relevance, *OJ L* 174, 1.7.2011, pp. 74–87

³ European Commission. New safety features for medicines sold in the EU - Questions & Answers, Available on http://europa.eu/rapid/press-release_MEMO-19-802_en.htm. Accessed June 04, 2019.

is a part of a comprehensive drug testing system, introduced by the new legislation. Depending on the origin of the medicinal product, the wholesalers might also need to scan the medicinal products during its movement through the chain to verify its origin and batch, as well as pharmacies (even in hospitals) will have to do the same before dispensing the medicinal product to the patient⁴. To date, the main difficulties in dealing with counterfeit medicinal products are associated, firstly, with the fact that it is almost impossible to determine the real extent of their circulation in the market, since official statistics only reflect the number of detected counterfeit medicinal products. Secondly, the manufacturing techniques of counterfeit are improving every year, therefore, it is possible to distinguish a genuine product from a fake, only having special knowledge, experience and technologies. Thus, the only way to combat fraud is to take cardinal preventive measures that can not only make counterfeiting a non-profitable and unattractive business, but also completely exclude the possibility of falsifying original medicinal products. These measures should include the improvement of law enforcement agencies effectiveness in identifying and preventing the circulation of counterfeit medicinal products, toughening the responsibility for their production and circulation, modification of criminal legislation, and further improvement of legislation. However, the transfer from one system of control to another can put additional pressure to the producers and distributors, as well as endanger the patients' rights.

The aim of this paper is to analyse the impact of new falsified medicinal products' distribution prevention regulation on distributors and patients' rights in Latvia.

- In order to reach the aim, the following tasks have been set up:
- To analyse the literature review behind the problem of the falsification of the medicines.
- To analyse the background and the introduced updates to the new falsified medicinal products' distribution prevention regulation.
- To analyse the good distribution practice issues and operations of the pharmaceutical companies.
- To present the case analysis of the distributor in Latvia, based on the experience.
- To present possible conflicts and challenges which appear after the 9th of February, when the new regulation came into force;
- To drive conclusions about patients' rights and falsified medicinal products' distribution.

Hypothesis of the thesis is as follows: implementation of the new falsified medicinal products' distribution prevention regulation puts additional not reasonable economic pressure on the pharmaceutical companies and other distributors, as well as may be a basis for legal conflicts.

Research questions of the thesis are as follows:

[RQ1]: What are the background and benefits of the new European Union prevention regulation of the entry into legal supply chain of falsified medicinal products?

[RQ2]: What are the updated or newly created duties of the pharmaceutical products distributors?

⁴ European Patient's Academy. Falsified medicines, Available on <https://www.eupati.eu/safety-of-medicines/falsified-medicines/>. Accessed June 04, 2019.

[RQ3]: What are the conflicts and problems pharmaceutical products distributors face while implementing the new requirements set by the updated regulation?

The research is descriptive by its nature, as well as the study is causal, establishing the cause-and-effect of new regulation coming into force. The study is non-contrived, while the researcher did not manipulate the variables. The study is longitudinal, while the author presents the changes in legislation over time. The research is qualitative, the researcher interference is minimal. The study has some limitations, while the researcher had limited amount of time to study all the relevant legislative background, therefore used the major documents as well as summaries presented by other researchers.

1. EUROPEAN UNION PREVENTION REGULATION OF THE ENTRY INTO THE LEGAL SUPPLY CHAIN OF FALSIFIED MEDICINAL PRODUCTS

Medicinal products' falsification issue has been noted as long as the pharmacy has been transferred into a business. The limited terms of production, limited shelf life, and other features of the medicinal products for human use, made it economically profitable to produce and import the falsified medicinal products, while the falsified medicines usually possessed the shorter route from the production to the end user, making the financial cash flow turnover rapid. Moreover, the falsified products were also produced in rather small batches directly in the pharmacies, that made it almost invulnerable to the inspection of the regulatory authorities. Even more to add, if the falsified medicinal product for the human use did not create the expected therapeutic effect, it was always possible to refer to the fact that every patient reacts differently to the medicine. This tendency was supported by the free market as well as by the disparity between the real supply of the medicines for human use of different types and the effective demand for it. Often specific medicinal products, that are in high demand of the society, are either not available on the market due to the various political and economic reasons, while the own industry of the country is not developed and imports are not allowed or are not economically reasonable for the importer due to high regulatory requirements and registration costs, or the unreasonable customs duties, or due to inadequate pricing policy under the pressure of economic or political conditions, resulting in too high shelf prices, that are not acceptable for the mass market. In the modern economic conditions, the costs for overcoming the barriers or enter the market, creating the path of the medicinal products to the consumer, are often too high for the importer, that creates the certain opportunity for the producers of the falsified medicines. Usually the low price is the main cause of the immortality of true and imaginary falsifications of the products of all times. Still, the amounts of the falsified medicinal products for human use reached too high levels, leading to the World Health organisation to drive its attention to the case in the end of 20th century. In this chapter author presents the detailed analysis of causes for the falsification of the medicinal products for human use, as well as presents the background behind the new regulation of the European Union regarding the prevention of the entry into legal supply chain of falsified medicinal products for human use.

1.1. Problem of the falsification of medicinal products for human use

According to the World Health organisation there are three types of medicinal products for human use that may be defined as falsified. These are as follows:

Substandard, that are also so-called «missing the specification» medicine, that are authorized, but still not completing one or more quality standards or specifications, mentioned in the registration dossier of the medicinal product. Registration dossiers, are the standards of each specific medicinal product, that has been officially approved by the regulatory authority. In case of European Union this institution is either European Medicines Agency (regional regulatory authority) or Medicines Agency of each member state (national regulatory authority).

Unregistered or unlicensed medical products for human use that have not been either submitted or approved by European Medicines Agency (regional regulatory authority) or Medicines Agency of the member state (national regulatory authority) for the specific market

they have been marketed to. Sometimes it is subject to the national permit, then this permit has to be approved and referred to the national or regional regulatory authority.

Falsified medical products for human use which fraudulently misrepresent composition, source, brand or identity. Falsified medicines are not counterfeit medicines, while counterfeit ones are medicinal products that do not comply with intellectual-property rights or that infringe trademark law.

As soon as the unregistered medicines for the human use are sometimes the subject of the exception, the majority of the regulatory authorities were mainly concerning the substandard and falsified medicinal products as the “falsification”, that created the definite misunderstanding in the various countries and lead to the rise in the level of distribution of the products approved on one market to the markets they have not been licenced for. Let author next concern the typed of the falsified and substandard medicinal products and the problems caused by the distribution. First, one of the typed is the placebo medicinal products, that are marketed without any active substance, that is replaced by the neutral substance, like lime, talc and soda. These medicinal products do not have any impact of the condition of the end user. Second, medicinal products “imitators” appear, where the active substance is replaced by the other ingredient, that is less costly, but may have the other therapeutic impact or adverse reactions. This type of the medicinal products is dangerous for the health of the patient, while the unpredicted reaction might be caused. The third type includes those medicinal products for human use that contain the same active ingredient, only in a greater or lesser amount. It does not bring direct harm to the health of the end consumer, but the effect will be somewhat changed. Since cheap substances and excipients may be of poor quality, then a large amount of technological impurities (uncontrolled by the standards) with an unpredictable toxic effect may be present in the finished product formulation. Unknown composition and production technology of the falsified medicinal products can lead to the risk of non-bioequivalence (too fast or too slow release of the active substance, that can cause respectively overdose and adverse reactions or insufficient efficiency, form resistant strains of microorganisms (in the case of antimicrobial medicinal products). Summing up, any falsification of medicinal products for human use is considered a threat because the quality control due diligence has not been performed.

The quality of the medicinal product is a set of properties that give the specific medicinal product for human use the ability to satisfy the end user (patient) in accordance with the purpose and comply with the requirements established by law. Usually, the quality of the medicinal product consists of three levels of compliances:

The effectiveness and safety (similar to benefit/risk ratio) of the most active pharmaceutical ingredient. The doctor and the patient are aware of differences in the efficiency and make the choice when prescribing and buying the specific medicinal product.

The requirements for the quality of the specification for the substance and finished medicinal product, as well as the level of development, production and quality control of the medicinal product (for example, compliance with the Good Manufacturing Practise requirements), which forms the difference in quality between different manufacturers of the same products, that affects the efficacy and safety. One of the main criteria for product specification quality check is the compliance of the medicinal product specification requirements with the requirements of the pharmacopoeia, which establishes the state quality standard for drugs.

The compliance of a specific sample of the medicinal product for human use with the requirements of its own specification (which is part of the registration dossier). The product that does not meet the requirements of its specification is considered substandard. Unlike the first two levels, the consumer is not aware of the compliance with the third level of quality, that created the possibility of falsification.

The proposed classification demonstrates the complexity and ambiguity of the concept of the medicinal product quality due diligence control.

In the end of 1984, the amounts of the falsified medicinal products for human use reached the enormous level, that is why in Nairobi in 1985, with the support of the WHO, took part the first worldwide Conference of Experts on the rational use of medicinal products. The aforementioned event was the first conference, where the national drug policies were discussed in details, as well as the procedures of changes, prescription practices, promotion and distribution had been discussed. Since then, the procedure of the introduction of the regulation regarding the prevention of distribution of falsified medicines has been actively introduced.

WHO suggests that pharmaceutical industry has a crucial role in the control, detection and destruction of falsified medicines for human use, which, according to the World Health organisation, can be performed by the development of protection systems (protective labels) in the way, allowing to prevent the falsification of the products, as well as preservation of drugs and packaging materials warehouses from theft. Regular research of own and national distribution channels according to WHO is mandatory in order to detect falsifications. WHO emphasized, that it is necessary to urge medicines' manufacturers who have been subjected to falsification to voluntarily disseminate such information through national authorized medicines quality control authorities and government officials, aimed at monitoring the compliance with laws in order to use it as an evidence in legal proceedings⁵.

1.2. Background of the regulation aimed at prevention of distribution of the European Union

The legal framework for the regulation of the medicinal products' market was established in 1965 via the Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law⁶, regulation or administrative action relating to medicinal products. In subsequent years, the legislation of the European Union actively developed through the adoption of dozens of other directives, decisions and resolutions of the governing bodies of the European Union, including the Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products⁷, as well as a number of other provisions, that have been specifically introduced for the proprietary medicinal products, immunological medicinal

⁵ World Health Organisation. Substandard and Falsified Medical Products, available on: <https://www.who.int/news-room/fact-sheets/detail/substandard-and-falsified-medical-products>. Accessed April 19, 2019.

⁶ Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products, OJ 22, 09.02.1965, pp. 369–373

⁷ Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products, OJ L 147, 9.6.1975, pp. 1–12

products consisting of vaccines, toxins or serums and allergens, medicinal products derived from human blood or human plasma. In the earliest 1990s some additional legislative framework has been introduced, like Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use⁸, that was one of the first European Union documents, regarding the wholesaling of the products, as well as the Council Directive 92/26/EEC of 31 March 1992 concerning the classification for the supply of medicinal products for human use⁹. The same time the regulations on the labelling, promotion and marketing have been introduced widening the scope of Directives 65/65/EEC and 75/319/EEC.

At the beginning of the new century, the previously existing regulations were revised and replaced by a single code by the Directive 2001/83/EC of 6 November 2001¹⁰. The directive laid down all the fundamental principles of market entry (registration), production and pharmacovigilance of registered medicinal products, especially for human use. Exactly this directive created the basis for the existing updated regulation on the falsified medicinal products for human use, while it contained the fundamental standards for confirming safety and efficacy, as well as the need to prove a positive balance between the benefits and risks of a drug. The Directive contained all registration procedures including registration grounds (original / reference product, replicated, hybrid, biosimilar product, established drug use, fixed combination, and other), production issues and Good Manufacturing Practise issues, drug information issues (labelling), wholesaling and Good Distribution Practise issues, conditions for release, advertising, pharmacovigilance, as well as supervision and sanctions. Moreover, the appendix to the directive contained requirements for the dossier of medicinal products registered on a different legal basis, that was a first try to eliminate the risk of unregistered or unlicensed medical products for human use to be marketed on non-specified market. In addition, this Directive became more detailed, contained more clarifications and was more precisely written (and translated). It allowed a better interpretation of the European Union requirements.

Still, as a result, there was a necessity on the even more detailed regulation of the medicinal products, that is why the Directive was amended step by step in the majority of the aspects, providing new grounds. Overall, it was amended by the following directives and regulations:

- Directive 2002/98/EC of the European Parliament and of the Council of 27 January
- Commission directive 2003/63/EC of 25 June 2003 L 159 46 27.6.2003
- Directive 2004/24/EC of the European Parliament and of the Council of 31 March
- Directive 2004/27/EC of the European Parliament and of the Council of 31 March
- Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006
- Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November

⁸ Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use, *OJ L* 113, 30.4.1992, pp. 1–4

⁹ Council Directive 92/26/EEC of 31 March 1992 concerning the classification for the supply of medicinal products for human use, *OJ L* 113, 30.4.1992, pp. 5–7

¹⁰ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, *OJ L* 311, 28.11.2001, pp. 67–128

- Directive 2008/29/EC of the European Parliament and of the Council of 11 March
- Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009
- Commission Directive 2009/120/EC of 14 September 2009
- Directive 2010/84/EU of the European Parliament and of the Council of 15 December
- Directive 2011/62/EU of the European Parliament and of the Council of 8 June
- Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012
- Directive 2011/62/EU of the European Parliament and of the Council was the latest updated version devoted to the prevention of the falsified medicinal products' for human use¹¹, that created the ground for the modern regulations, which will be seen in the next subchapter.

1.3. Updated directive and delegated regulation of the European Union

In 2011, EU Directive No. 2011/62/EC was adopted to amend Directive No. 2001/83/EC to ensure the safety of medicinal products and prevent falsifying¹². In 2016, the Delegated Regulation 2016/161 was adopted, which is an addition to the Directive of the European Parliament No. 2001/83 / EC in the parts that have been amended by Directive No. 2011/62/EC¹³.

According to the documents, all EU member states are obliged to bring their own legislation and trade practices in line with the requirements of this directive until February 9, 2019. It is important to note, while the updated requirements implied that protection against the falsification of the medicinal products is carried out by applying a special unique number on the packaging, which will allow to distinguish falsified medicinal products from the original ones, since the unique number of each package can be checked at any time using a special database on the European and national levels. The new regulation uses two-dimensional codes that are designed to encode a large amount of information. The decoding of such a code is carried out in two dimensions (horizontally and vertically). It is emphasized that all prescription medicinal products registered in the country and some non-prescription ones (right now only one - Omeprazol), must be labelled with a unique identifier by the manufacturer.

Germany was chosen as the country for the implementation of the pilot project, that was defined as successful. Moreover, in addition to the fact, that a package of the product must bear a unique serial number to identify and confirm the authenticity of each product, it must be also sealed in such a way that there are obvious marks on it when attempting to open it.

¹¹ 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 Text with EEA relevance, *OJ L* 174, 1.7.2011, pp. 74–87

¹² Ibid.

¹³ 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 (Text with EEA relevance), available on: <https://emvo-medicines.eu/new/wp-content/uploads/Delegated-Regulation-EU-2016-161.pdf>. Accessed April 19, 2019.

Consequently, the details on which institutions are going to control authenticity of medicinal products and the way how it will be performed, as well as the characteristics of various protection options in the final version were published in the Delegated Regulation of the EU Commission 2016/161¹⁴. According to the Directive the serial numbers and the integrity of the package of the medicinal products are monitored at distribution points, at production and during the movement of the package. The serial numbers are checked via the national database, and the integrity of the packaging is determined visually adding the requirements to the Good Distribution Practice guidelines.

Pharmaceutical companies, their subcontractors, wholesalers and pharmacies were involved in the implementation of the solution. Falsified medicinal products have to be quickly detected and removed from traffic without incident. Manufacturers who do not have such a tracking solution will have to withdraw their products from the European market. The existing solution (proved in the test project) called Datamatrix stores a large amount of information in a small space, the potential of reading is better than a traditional barcode. The tightening of regulations, dictated by the fight against falsification of medicinal products, requires measures of maximum security throughout the supply chain in the manufacture of pharmaceutical products. Serialization (meaning the check of all “series” or batches of the medicinal products) for the purpose of reliable product tracking became the decisive means of ensuring quality and safety. Therefore, at each stage of production and packaging, medicinal products for human use are printed with data that allows them to track products along the chain from the manufacturer to the customer¹⁵. Similar initiatives are being implemented in pharmaceutical production in other countries of the world, for example, in the USA, China and Brazil, still in the majority of them are not yet fully implemented. Manufacturers of pharmaceutical products in these countries also must supply all products and packaging with unique traceable serial numbers.

The main idea of the traceability mechanism in the EU is the practice of "step back - step forward". It is understood as a system in which each participant in the supply chain can provide information about the origin of the medicinal product and its further movement. Thus, producers and distributors themselves must control and identify to whom they supply and from whom they purchase products throughout the entire chain, updating the requirements of the Good Distribution Practice guidelines.

In addition, on January 1, 2016, the European Convention called Medicrime entered into force, providing for criminal liability for falsifying and counterfeiting of medicinal products, their illegal production and similar crimes that pose a threat to public health. This convention is the first international document that obliges all signatories to bring to justice those responsible for the deliberate falsification of medicinal products, relevant documents, trade of the falsified products¹⁶.

¹⁴ 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 (Text with EEA relevance), available on: <https://emvo-medicines.eu/new/wp-content/uploads/Delegated-Regulation-EU-2016-161.pdf>. Accessed April 19, 2019.

¹⁵ European Commission. Safety features for medicinal products for human use, available on https://emvo-medicines.eu/new/wp-content/uploads/qa_safetyfeature_en_V13.pdf. Accessed April 19, 2019.

¹⁶ Council of Europe. Council of Europe Convention on the Counterfeiting of Medical Products and Similar Crimes Involving Threats to Public Health. MEDICRIME Convention. (2011) Available on: <https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/211>. Accessed April 19, 2019.

2. GOOD DISTRIBUTION PRACTICE FOR PHARMACEUTICAL COMPANIES: ORIGINS AND AIMS

The Good Distribution practice (GDP) is a quality assurance system for warehouses and wholesaler companies in the circulation of medicinal products. According to internationally accepted GDP rules, distributors of medicinal products must align their activities with these standards. The implementation of GDP rules ensures the availability of consistent quality management systems throughout the supply chain: starting with the delivery of raw materials to manufacturing plants and ending with the shipment of finished products to end customers. Independent assessment is the most effective way to confirm that the quality management system complies with international GDP requirements. The GDP Standard establishes a unified approach to the organizational process of the wholesale distribution of medicines and is aimed at ensuring the quality of products from the manufacturer to the retail network and medical institutions. It is based on the principles of good distribution practices adopted in the European Community and recommended by the World Health organization. Compliance with this standard ensures: quality and safety of medicinal products and medical equipment guaranteed by the manufacturer; the flow of medicines, medical equipment and medical products without changing their properties in the retail network and the retail health organizations. The purpose of the standard is to preserve the quality of the product as it moves from the manufacturer to the consumer, that is why the GDP is fully interconnected with the updated regulation.

2.1. Current situation on the GDP in the pharmaceutical industry

As in the globally accepted GDP, the EU standards apply to everyone in the European Union who participates in the wholesale distribution of medicinal products. As mentioned above, GDP regulates all stages of the movement of medicines and pharmaceutical substances along the distribution chain - from manufacturers' warehouses to pharmacies and medical institutions. Its goal is to observe proper storage, transportation and distribution conditions to ensure the quality, safety and efficacy of medical products, as well as to prevent falsified medicines from entering the EU market. In addition, the Practice define a number of approaches to the company of distribution of medicinal products in the EU, which allow them to follow the movement and ensure the continuity of the distributor's responsibility for maintaining the declared quality of the medicinal product¹⁷. In this regard, in particular, it establishes the mandatory metrological control of the temperature regime at the implementation stages, introduces the concept of a "responsible person", whose competence includes the creation and maintenance of a distributor quality assurance system, work with reclamations and product reviews. So, for example, when complaints arise, it is necessary to examine the entire supply chain of goods from the manufacturer to the patient. Moreover, a system of bilateral audits is established both by the distributor and by the manufacturer, and in the opposite direction. The major aim of implementation of the GDP standard is to preserve medical products' quality and integrity, provide the inhabitants of the EU countries with the

¹⁷ World Health Organisation. WHO good distribution practices for pharmaceutical products, available on: http://academy.gmp-compliance.org/guidemgr/files/GDP_TRS957Annex5.pdf. Accessed April 19, 2019.

products which quality, pharmacological properties and claimed effectiveness remains the same during the delivery process from the manufacturers to patients¹⁸.

Let author list below the benefits from the introduction of the GDP standards to the company, both in business and legal terms: The GDP introduction aligns the company's business processes according to the quality assurance system, as well as let the allocate resources and staff efficiently. In addition, the GDP supports the brand of the company, ensuring trust and confidence in partners and consumers, as well as automatic compliance with the regulations of the country or the EU. In addition, GDP introduction improves the quality and safety of products and ensures the successful competition in public procurements, supplier selection procedures, being compliant with the legal requirements of the Member states.¹⁹

2.2. Updated duties of the pharmaceutical companies

The EU Directive No. 2011/62/EC introduced new obligations for wholesalers, which concern standards in the quality system, personnel training and hygiene, facilities and equipment, documentation, thus updating the Good Distribution Practice.

The revised guidelines mostly presented the changes in the following aspects:

- Revised risk management principles, creation of the standart operation documentation, process and risk management in the company;
- Revised requirements to the premises, installations, equipment, to ensure proper storage and distribution of medicinal products;
- Revised requirements to the management of complaints, returns, suspected falsified medicinal products and recalls of the medicinal products;
- Revised transportation rules to protect the products against theft, loss, breakage, failing temperature conditions;
- Specific rules for brokers (person involved in activities in relation to the sale or purchase of medicinal products)²⁰.

There are new requirements for the equipment, especially computerised systems, as the subchapter 3.3.1 of the Guidelines require the validation or verification of all systems that are proving that the system is capable to achieve the necessary results, with all the tests included. The companies should also provide a document which has to state all computer systems used within a company and describe the principles and features of interaction of all these computer systems. Moreover, the hardware and equipment should also be validated and in case if any maintenance or change occur, the new validation and new tests should be performed, after which the new document has to be presented²¹.

All the products should be checked via the national database, where the producer of the product has to upload the information about each package produced. When arriving to the wholesaler, the batch of the medicine has to be verified in order to avoid the potentially

¹⁸ Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use, *OJ C* 343, 23.11.2013. Available on <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:343:0001:0014:EN:PDF>. Accessed April 19, 2019.

¹⁹ Good distribution practice, available on: <http://iso-bel.com/gmp>. Accessed August 18, 2019.

²⁰ Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use, *OJ C* 343, 23.11.2013. Available on <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:343:0001:0014:EN:PDF>. Accessed April 19, 2019.

²¹ *Ibid.*

falsified products in case when medicinal products arrived directly from the producer. In case when medicinal products, that are under the regulation of the new Directive, have been brought from other source, not directly from the producer or its representative, the wholesaler has to verify each package from the batch. All the records of verification and the potential threats if any have to be stored. In case of the product recall from the market, if product is returned or suspected - the wholesalers in the whole distribution chain have to verify (scan) each package of the product again. Distributors and representatives of the producers are also responsible for marking a package if the product is quarantined, removed from sales as a sample for testing, and other similar activities. In addition to all the aforementioned activities the wholesalers and the producers should be connected to the national database, to have developed documentation and standard operations on the validation of all the processes, systems and equipment used.

During the operations the distributors have to manually check two safety signs which are mandatory to be presented on the packaging - a two-dimensional bar code or a unique identifier and an unauthorized opening indicator which ensures the authenticity of medical products in the interests of patients and enterprises, as well as strengthens the security of the medicines' in supply system. All pharmaceutical companies must be connected to the database²².

Implementation of this system in Latvia required a radical improvement in the IT infrastructure (computers and Internet access points) which resulted in substantial financial costs for manufacturers (installation of additional equipment, modernization of packaging lines, installation of track & trace systems), distributors and pharmacy chains (software, scanners, staff training). Regulatory access to the database is also a separate aspect of the implementation of this project and had to be agreed at the initial stages.

²² European Commission. Delegated act on the detailed rules for a unique identifier for medicinal products for human use (Tech. No. 1342823), available on https://ec.europa.eu/health/sites/health/files/files/falsified_medicines/2012-06_safety-features/blue_sphere_en.pdf. Accessed April 19, 2019.

3. CASE ANALYSIS OF THE DISTRIBUTOR IN LATVIA

In this chapter it is planned to observe the distributor in Latvia, which has been affected by the changes in the regulation. The company is mainly operating with the other the counter (OTC) medical products from Germany and Czech Republic, still it also deals with a number of various prescription medicines, coming directly from the producers in Slovenia. The company portfolio includes around 55 products, being marketed around Latvia, which have to be controlled under the legal framework of the updated regulation.

During the on-boarding to the national hub, where the data is stored, and connection to which is obligatory, the company had to choose a technical partner, who will provide an IT solution to the company. During the analysis of various IT providers presented on a market, the company has detected that the majority of the providers offer similar cloud-based solutions, including the storage of all the recorded data and the connection to the national hub. The costs were similar; therefore, the company management preferred the cooperation with one of the IT companies (referred as - Developer) having developed the European server network and EU hub in 2011-2016. Data is kept in a database provided by the Microsoft "Azure" cloud service. The database is hosted in a Microsoft computer centre inside the European Union. Developer manages and administers the database. Access to the data is possible through the web application. On the one hand, this constitutes the control centre, which can be retrieved through a web browser (recommended: Google Chrome), on the other hand, the web application forms the interface to the business application (available for Android, Windows, iOS). The business application is installed and executed on devices (e.g. scanners, terminals or smartphones). Developer provides the business application in the form of an installation file (Windows) and/or an Android package kit file.

Verification and decommissioning (all processes of sales, goods removal from the flow, is considered as decommissioning) processes can be planned, controlled, executed and evaluated with the application presented by the Developer. Use occurs through registered users of the company. The application is subdivided into two components: the control centre and business application. Execution of the verification and decommissioning processes occurs through scanning of the medicine packs using the business application. The control centre provides both the functionalities for administration (device management, user management, etc.) as well as transaction-oriented functionalities (release process for bulk transactions, communication with the national verification systems, etc.).

In order to provide the compliance with the legal requirements, medicines are scanned individually or in a bulk with the business application in single transaction process verification. The employee (a user) can scan new barcodes (only 2D data matrix codes) via the selection in the business application on the screen of the scanning device. After scanning, the application communicates with the national verification system and the user receives an immediate report on the status of the medicine. The employees of the distributor scan the packages in all cases, including the theft and destruction. However, all the procedures, except for theft and destruction, can be cancelled in case of the reversed transaction.

As required by the updated regulation, all historic transactions are stored in the archive. The structure is similar to the transaction overview. In addition, the user can set filters to make targeted searches for transactions. Possible filters are: GTIN, expiration date, product number, batch number, status, process type, date range. In the archive, data is stored

at most up to an age of 12 months as requested by the Directive; older data is being deleted automatically.

As the company operates directly with the producer, it is necessary to perform the following actions:

- To verify medical product through scanning one package per batch on the incoming flow, in order to secure the status;
- To dispense through scanning (decommission) the products, when selling the products to the social cancers, small medical assistance points, paramedic points, prison hospitals, social support centres. While these institutions are not able to finance the connection to the hub, the sellers instead of the receivers are responsible for the validity of the medicinal product;
- To mark through scanning the returned medicinal products, broken medicinal products, medicinal products used for tests or samples²³.

As the number of the aforementioned transactions for the company was not high, it was decided to create five users for the scanning and two users in the control department. Taking into account that given company is operating only on the Latvian market, the national interface required was the Latvian National hub.

The company selected employees for each user group. User groups are:

- Power administrator - This administrator has full authorization across all locations of the entire company
- Location administrator - This user has all necessary authorizations for a specific location
- Control centre user - This user may not edit any master data but only view it. Furthermore, he/she may call up the transaction overview and display transaction
- Business application user – This user has access only to the business application and conducts all relevant verification and decommissioning processes.

All the software and hardware had to be validated as well. Company had to create a set of standard operations according to the new requirements of the inflow and outflow of goods. The validation documentation was purchased from the Developer, as the company was unable to proceed with the validity and control system tests as required by the EU regulations by itself. Therefore, the following documentation was transferred to the company together with the transfer of the application:

1. User documentation for the control centre
2. User documentation for the business application regarding the processes
3. Installation documentation for administrators of the control centre and business application
4. Validation documents

As presented in the table below, the initial investment of the company was € 20,000 in total plus the monthly costs are € 579, which results in € 6936 per year. In addition to that, the

²³ Grozījumi Ministru Kabineta 2007. Gada 26. Jūnija Noteikumos Nr. 416 "Zāļu Izplatīšanas Un Kvalitātes Kontroles Kārtība (Amendments to the Cabinet of Ministers Regulation No. 26 of June 26, 2007 416 "Procedures for Distribution and Quality Control of Medicinal Products) (02 February 2016) Available on: <https://likumi.lv/ta/id/304322-grozijumi-ministru-kabineta-2007-gada-26-junija-noteikumos-nr-416-zalu-izplatisanas-un-kvalitates-kontroles-kartiba->. Accessed April 19, 2019.

company had to invest about € 3000 in the hardware and € 2000 in the training of the employees, as stated above, the Developer provides only initial training. Due to the rather low amount of transactions, the company did not need to hire more employees or acquire additional assets (computers or professional scanners, costing up to € 4000 per item).

Table 1

Company costs

Description	Value in €	Invoicing cycle
Activation fee	€ 5,000	One-time
Starter package Users: 5 NMVS interface: 1 ²⁴ Storage location: 1	€ 499	Monthly
Additional services		
Users	€ 39	Monthly
Interfaces for national systems	€ 99	Monthly
Storage locations	€ 199	Monthly
Additional services incl.: - Project Management - Creation of Qualification Documents -Test execution -Initial Training	€ 1.250 per day (12 days in total)	One-time

Summing up, the initial investment € 25,000 and € 6936 as yearly costs are, according to the company data, hardly covered by the income of the company, while the majority of the medicines are sold directly to the state institutions with the loss or with the wholesalers controlling the pharmacy chains with the minimal mark-up, while the prescription medicines mark-up is managed and set up by the national regulations. It means that the company will face the necessity to cover the expenses by the changes in the OTC medicinal products' prices introducing the financial pressure on producers, distributors and end users. In the next chapter, the challenges and problems will be analysed, based on the experience of the company in this case analysis.

²⁴ EMVO. EMVO Fee model 5.13, available on: from https://emvo-medicines.eu/new/wp-content/uploads/NMVO_FEE_MODELS_V5.13.pdf. Accessed April 19, 2019.

4. POSSIBLE CONFLICTS AND PROBLEMS DURING THE IMPLEMENTATION OF THE NEW FALSIFIED MEDICINAL PRODUCTS' DISTRIBUTION PREVENTION REGULATION

4.1. Challenges pharmaceutical companies and another distributors face

Firstly, let author analyse the information, acquired from the company from the previous chapter, while conducting the company performance analysis. In the last months of operation, the company faced a number of problems:

1) Failure of the EU hubs performance. In the first month when the regulation came in force, the European Union IT infrastructure was detected as not ready to perform correctly with given number of transactions and users. The hub was offline part of the time, meaning that the national verification systems were not able to connect to the hub in the order to check and exchange the information, the producers could not upload the necessary data, as well as the distributors were almost not able to check or dispense the medicinal products. Disregarding the fact that this issue was unpleasant, it was mostly solved by the producers and distributors, who have predicted the possibility of the system failure and hedged the risks by ordering, producing and importing the medicinal products before the 09th of February, to secure availability of necessary medicinal products on stock for one or two months ahead, until the IT issues would be solved. However, the drop in sales was already noted, as while the producers were trying to comply with the requirement they were not able to move the goods in a regular amount, therefore the financial ratios also dropped²⁵.

2) Update of the documents. In order to comply with the renewed GDP requirements and new requirements set by Directive on the prevention of the falsified medicinal products, the companies had to update all the standard operations and other documents. All the documents were formed according to the international and national norms. Taking into account that the national norms were not accepted until the beginning of 2019, the vast number of companies had to update their documents twice, first time documents were prepared according to the new international regulations and second time, according to somewhat tightened national norms.

3) The technical impossibility of applying an individual code. It was a problem for the number of producers to apply the code to existing packaging due to its small size or inappropriate shape. This resulted in the wrong placement and disability of the distributor to scan the package in an ordinary way. Moreover, scanning of each package is time-consuming, adding to this a fact that the response from the European hub is slow and it takes time to receive an appropriate report, using new system the time of operations increased almost twice. In the way to ease the scanning procedure, the companies have to invest in professional scanners as well as create additional space for the scanning with the appropriate lighting, that will consequently affect the documents and standard operations.

4) Scanning failures. This issue was claimed to be the most serious and risky and is investigated by the national and EU agencies. Part of the uploaded data by the producers is not correctly represented on the international and/or national data storage levels. This occurs

²⁵ EMVO. Letter of announcement: Downtime and Disruption Information System (DDIS), available on: https://emvo-medicines.eu/new/wp-content/uploads/EMVO_LoA_0051_20190201_DDIS-update.pdf. Accessed April 19, 2019.

due to the lack of several features, that in some repositories are mandatory, but in others - are not, as well as due to the technical misclicks and similar issues. These cases are consequent and are repeating almost every week, urging the distributors to move the packages to the quarantine area and not being able either to return, or to sell the medicinal products, even despite the fact that the medicinal products are not falsified, are approved by laboratory, and even in case of the reimbursed medicines or medicines for the hospitals, that are urgently needed for patients in critical conditions. Trying to solve these issues the companies were usually reported that the problem is on the data repository level and the companies have to quarantine the product until a problem is solved. This occurs also due to the challenge for the manufacturers to report on the volume of production of medicines in advance and buy the unique codes for each batch from the European hub, which is not always possible in the conditions of market volatility and demand for it.

Furthermore, it is necessary to present some other issues, that have been experienced by the representative offices of various brands in Latvia, other distributors and pharmacies.

One of the small pharmacy company reported, that as soon as the company was not a part of any big pharmaceutical holding (the number of pharmacies in the company is three), it had to follow the changes in the regulations by itself. The major problem for the implementation of the new requirements was the lack of information for the company. After a number of meetings with the Latvian National Medicine Verification Agency it was concluded, that every pharmacist of the pharmacies has to verify every package upon arrival from the distributor to check the validity of the package. Similarly, when selling the package to the end customer, the employee has to scan (dispense) the package. The company could use the opportunity to verify the medicine only in one of three pharmacies, but the companies did not have a common logistics system, therefore each of the pharmacies had to separately manually enter the information about each package having entered in the circulation by itself. This increased the working time of the employees and created the necessity to hire additional staff, also, scanning via mobile devices in the pharmacies is not acceptable due to the time constraints, therefore the professional scanners were purchased. Taking into account the fact, that the monthly turnover of the company is less than 15 thousand euro, and the total investments in new system with activation fee of more than 20 thousand euro lead to question if existence of this type of small pharmacy chains are reasonable.

Next, the responsibility for the small medical assistance centres and other social centres, that cannot afford such huge investments seems to be biased. The state is unable to support social institutions and transfer the responsibility to the business sector, whose payments form the budget for the social establishments. Moreover, the small pharmacies and private companies are not able to comply with all requirements as well, up to now, no specific measures have been introduced to assist.

4.2. Legal conflicts

Taking into account the issues mentioned in subchapter 6.1, the importers and responsible institutions are unable to ensure the presence of the medicines on the market timely. To discuss this situation in terms of the possible legal conflicts, let author first present the legal framework behind the rights of the patients. According to the Universal Declaration of human rights set by the United Nations, every person, as a member of society, has the right to social security and to exercise the rights necessary for maintaining his dignity and for the free development of his personality in the economic, social and cultural fields through

national efforts and international cooperation and in accordance with the structure and resources of each state. This was followed by the consequent adoption of the Universal Declaration of Human Rights²⁶ and also in 1950 by the signature of the European Convention of Human Rights²⁷. Next, let author consider the legislation considering the responsibilities and duties of the states. In 1978 the Declaration of Alma-Ata stated that states have a responsibility for the health of the citizens and people living on the territory²⁸, which can be fulfilled only by the provision of adequate health and social measures. In 1994 the Declaration on the promotion of patient's rights in Europe²⁹ by WHO was published, stating that "everyone has the right to receive such health care as is appropriate to his or her health needs, including preventive care and activities aimed at health promotion. Services should be continuously available and accessible to all equitably, without discrimination and according to the financial, human and material resources which can be made available in a given society".

As to the EU legislative framework, then it is possible to state Convention for Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Biomedicine: Convention of Human Rights and Biomedicine, Council of Europe as the one of the primary documents, that Latvia has ratified in 2010. The Convention is the first legally binding international text aimed at protecting human dignity, rights and freedoms by adopting a number of principles and prohibitions against the misuse of the achievements of biology and medicine³⁰. The starting point of the Convention is that human interests are above the interests of science or society. The Convention sets out a number of principles and prohibitions in relation to genetic and medical research, consent, the right to privacy and information, transplantation, public discussion, etc. The Convention prohibits all forms of discrimination based on genetic heritage and permits genetic testing for medical purposes only. It permits genetic engineering only for prophylactic, diagnostic, or therapeutic purposes, and only on condition that such engineering is not aimed at changing the genome of the heirs of a given person. The Convention prohibits the use of technologies aimed at providing medical assistance in procreation in order to choose the sex of the future child, unless this is done to prevent the child from inheriting a serious disease.

The Convention establishes the rules of medical research, listing their detailed specific conditions, especially for those who are unable to consent to such research. It is forbidden to create human embryos for research purposes, and when a country allows research on embryos in vitro, adequate protection of these embryos must be provided.

The Convention also establishes the principle that a person must give the necessary consent for medical intervention in an explicit form and in advance, with the exception of an emergency. Such consent may be freely refused at any time. Medical intervention for persons unable to consent to it, such as children and those suffering from a mental disorder, can only

²⁶ Universal declaration of human rights, available on: <https://www.un.org/en/universal-declaration-human-rights/>. Accessed April 19, 2019.

²⁷ European Convention of human rights, available on: https://www.echr.coe.int/Documents/Convention_ENG.pdf. Accessed April 19, 2019.

²⁸ Declaration of Alma-Ata International Conference on Primary Health Care, Alma-Ata, USSR, 6-12 September 1978, available on https://www.who.int/publications/almaata_declaration_en.pdf. Accessed April 19, 2019.

²⁹ Declaration of the promotion of the patients' rights in Europe, available on: https://www.who.int/genomics/public/eu_declaration1994.pdf. Accessed April 19, 2019.

³⁰ Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, Treaty Nr. 164 (1997) Available on: <https://www.coe.int/en/web/conventions/full-list/-/conventions/rms/090000168007cf98>. Accessed April 19, 2019.

be carried out in cases where it can have a real and direct positive effect. Convention provides, that each patient has the right to familiarize themselves with information about his state of health, including information about the results of genetic testing. However, it recognizes the rights of the patient not to be informed about this. The Convention prohibits the removal of organs and other tissues from persons who are unable to give appropriate consent. The only exception is allowed under certain conditions for the removal of regenerating tissues (especially bone marrow), when the recipient is a brother or sister of the donor. The Convention recognizes the importance of promoting public debate and proper consultation on the above issues. The only restrictions may be prescribed by law and be necessary in a democratic society in the interests of public peace, the prevention of crime, the protection of public health and the rights and freedoms of others.

Consequently, to the Convention, in order to ensure a high level of protection of human health and a high level of service in European medical institutions, as early as 2002, the European Charter of Patients' Rights was prepared. It defines 14 basic rights of every person, therefore, they must be recognized and respected in every state. Rights are related to the duties and responsibilities that patients and caregivers must assume. The Charter can be used as a way to initiate patient rights protection activities, consisting of both prevention of rights violations and remedial measures³¹. Such activities, along with the courts, can be carried out by active civil organizations, official institutions and bodies - for example, ombudsmen, ethical committees or alternative dispute resolution commissions³².

Nys and Goffin (2011) identify three types of patients' rights: basic, such as privacy, social, such as reimbursement and access to health care, as well as consumer-based, such as to choose the provider of treatment³³. In addition to the mentioned before, the authors stated that patient's rights have developed in Latvia since 2010, when the Patients' rights office has been developed. Disregarding the fact that the law concerned some of the issues already since 1997, the Patient's Rights law came into force in 2010³⁴. The purpose of the law is to promote a positive relationship between the patient and the health care provider by promoting the patient's active participation in their health care, as well as to enable him / her to exercise and defend their rights and interests. This law on the national level assumes the patient has the right for a timely treatment. The medical institution at which the patient has contacted provides information on the possibilities and terms of receiving the treatment, as well as on other medical institutions where appropriate treatment can be obtained. The aforementioned law together with the Medical treatment law form the basis for the fulfilment of the basic rights of the patient³⁵.

Social rights, in line with the Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border

³¹European Charter of Patients' Rights, available on http://ec.europa.eu/health/ph_overview/co_operation/mobility/docs/health_services_co108_en.pdf. Accessed April 19, 2019.

³² Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, Treaty Nr. 164 (1997) Available on: <https://www.coe.int/en/web/conventions/full-list/-/conventions/rms/090000168007cf98>. Accessed April 19, 2019.

³³ Palm, W., Townend, D., Nys, H. "Patients' rights in the European Union: from recognition to implementation: Willy Palm".

³⁴ Pacientu tiesību likums (Law On the Rights of Patients) (17 December 2009). Available on: <https://likumi.lv/ta/en/en/id/203008-law-on-the-rights-of-patients>. Accessed April 19, 2019.

³⁵ Kolassa, E. "The Economic Contribution of Pharmaceutical Marketing", pp. 101-08.

healthcare³⁶, about the financing, access and reimbursement, are provided by the Cabinet of Ministers Regulations Nr. 899³⁷ on the procedure for reimbursement of the costs of purchasing medicinal products and medical devices for outpatient treatment as well as the Health Care Financing Law of Latvia³⁸. The reimbursement procedure includes a set of measures that enable the patient to purchase medicines and medical devices, the purchase of which, in accordance with the regulations, is partly or fully covered by the funds allocated for reimbursement of drug purchase expenses for the current year. The aim of the compensatory measures is to provide medicines and medical devices to as wide a range of patients as possible within the funds allocated for reimbursement, as well as to channel the lowest possible price and cost savings for compensated medicines and medical devices to improving patients' health and achieving treatment goals. The cost of purchasing medicinal products and medical devices shall be borne in full by the State for the patient who is recognized as poor or as an asylum seeker in accordance with the procedures prescribed by regulatory enactments, and who is entitled to reimbursement of the costs of purchasing medicinal products or medical devices³⁹. Taking into account the aforementioned issues and the second chapter of the thesis, the following legal conflicts arise:

- Patient's rights violations
- Conflict of interests in terms of GDP

Let author next elaborate on both issues in details to drive conclusions about the possible impact on the legal conflicts of the new prevention regulation.

For a start, it is necessary to note the possible conflict that arises from the violation of the rights of patients. As mentioned earlier, incorrect or incorrectly functioning system of validation of medicinal products lead to the fact that distributors or manufacturers are not able to deliver to the market those products that are not validated by the new system. This happens even if all certificates and laboratory tests are available - the product must be quarantined until the failure is completely eliminated and can be sold only with a positive response from the system, responsible for the verification of the medicinal product. One more to point out is the fact, that the products, that are controlled and tested by the new regulation is the prescription medicines. The prescription is the official prescription of the medicinal product in the prescribed form, issued by an eligible medical employee for the purpose of dispensing the finished medicinal product. As soon as prescription medicinal products are usually more concentrated as well as very specifically used, they are strictly controlled by the government. This means that prescription medicinal products are quarantined, which delays the delivery of controlled products to the market in a timely manner. It is necessary to take into account the fact that neither the manufacturers nor the distributors are able to urgently produce or store huge quantities of goods. As a result, since the state controls and monitors prescription medicinal products and their movement, there is a shortage of one or another drug in the market due to quarantine. In addition, many of the prescription medicinal products are included in reimbursable medicinal products or medicinal products procured for the needs of

³⁶ Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare, *OJ L* 88, 4.4.2011, pp. 45–65.

³⁷ Ambulatorajai ārstēšanai paredzēto zāļu un medicīnisko ierīču iegādes izdevumu kompensācijas kārtība (Procedure for reimbursement of the costs of purchasing medicinal products and medical devices for outpatient treatment) (31 October 2006) Available on: <https://likumi.lv/doc.php?id=147522>. Accessed April 19, 2019.

³⁸ Veselības aprūpes finansēšanas likums (Health Care Financing Law) (14 December 2017). Available on: <https://likumi.lv/ta/id/296188-veselibas-aprupes-finansesanas-likums>. Accessed April 19, 2019.

³⁹ Noteikumi Par Zāļu Cenu Veidošanas Principiem (Regulations on Principles of Pricing of Medicinal Products) (25 October 2005) Available on: <https://likumi.lv/doc.php?id=120074>. Accessed April 19, 2019.

emergency care and hospitals. It should be emphasized that hospitals and government institutions operate on the principle of public procurement. Accordingly, by announcing the public procurement and concluding an agreement with the supplier, the hospital or institution cannot quickly purchase a similar product in the event of force majeure. Accordingly, a number of problematic situations arise in connection with the quarantine: first, medicinal products for patients from the reimbursement list are not available in a timely manner, and similar ones are available for for additional payment; secondly, medicinal products for hospitals, prisons and other social and state institutions responsible for treating the population are not available in a timely manner; thirdly, medicinal products are not available, which should be delivered on time according to the public procurement contracts. In such situation, a violation of a number of patients' rights occurs, as well as a conflict of interests and restriction of the distributor's freedom. In this case, the basic rights of the patient are violated, while the patient cannot choose the therapy or medicinal product, cannot choose the treatment, he is facing the limited choice. In addition, the social right of the patient is limited. The patient cannot claim reimbursement in the required amount, he is obliged to invest personal financial resources in order to continue therapy, and in case of a shortage of financial resources his right to access health care is limited. Similarly, the social rights of patients who are admitted to hospitals, where there are no medications to be provided by the state, are limited. Consumer-based rights of the patient are also violated, while the patient has to choose the provider of the therapy, who is able to provide the medicinal product, while the access to the medicinal products are not equal. The patient cannot choose the pharmacy, while in case of the computer failures, he has to choose the pharmacy with the more updated technical support, otherwise the medicinal products cannot be dispensed.

In addition, there is a conflict of interest between the manufacturer, state buyers, distributors and patients. Medical institutions that have concluded a contract with distributors have the opportunity to claim compensation or a fine if the goods are not delivered. In turn, when the verification system fails, the distributor does not have the right to make deliveries, but this happens not through his fault, but because of failures in the international information system. Accordingly, a situation where the distributor may incur losses arises, the hospital incurs losses and does not fulfil obligations to patients, and the rights of patients are limited. Such situations impose an additional financial burden on the distributor, together with losses and a heightened profit, which he incurs because of the impossibility of selling goods.

Violations of patient's rights or lack of attention to them can have serious health consequences. Such type of the hidden discrimination in healthcare is a powerful barrier to access to health services and affects their quality.

The second point that needs to be considered is a possible conflict of interest within the framework of the requirements of good distribution practice. This is another challenge distributors and medicinal products manufacturers meet. Any quarantine means constant communication with the responsible authorities for a quick solution to the problem. According to the standards of good distribution practices laid down in its fundamentals, the distributor can distribute in the interests of the public, provided that he is confident in compliance with the quality and all documentation required is present in the necessary form. Accordingly, subject to obtaining the necessary results of laboratory tests, certificates of production, and other data, the distributor can distribute the goods. However, on the other hand, even with the confidence of the validity of the medicinal products, the distributor cannot sell or transfer the medicinal products, since the medicinal products are incorrectly

displayed in the verification system. At this stage, most manufacturers and distributors put new regulations above the requirements of good practice, which requires further consideration.

In addition, work in accordance with good distribution practices, provides clearly marked movement of goods according to certain warehouse and logistics principles (e.g. first in - first out). It is stipulated that quarantine takes a long time, respectively, quarantine zones are far away in order to avoid goods mixing, as well as placing in quarantine requires the development of documentation and change of logistic processes. There is no concept of short-term quarantine, since the quarantine process is also regulated by pharmaceutical rules. However, new requirements do not provide for any other exclusion of goods from circulation, except by placing them in the quarantine zone. In turn, problems are often solved within one to two working days. Accordingly, since the company must follow the standards, a lot of additional processes are launched and carried out. Often such processes are completely unnecessary, while the company spends additional time and financial resources.

All of the above creates a conflict between the regulations of the pharmaceutical industry, the rights of patients and the new legislation. Insufficient preparation of the transition in Latvia has led to restrictions on the delivery of goods to the market and the inability to acquire them by patients.

CONCLUSIONS

After having conducted the research the author came to the following conclusions answering the research questions stated.

[RQ1]: What are the background and benefits of the new European Union prevention regulation of the entry into legal supply chain of falsified medicinal products?

1. At the beginning of the new century, the previously existing regulations regarding the marketing of the medicinal products were revised and replaced by a single code by the Directive 2001/83/EC of 6 November 2001.
2. The directive laid down all the fundamental principles of market entry (registration), production and pharmacovigilance of registered medicinal products, especially for human use. Exactly this directive created the basis for the existing updated regulation on the falsified medicinal products for human use, while it contained the fundamental standards for confirming safety and efficacy, as well as the need to prove a positive balance between the benefits and risks of a drug. Still, as a result, there was a necessity on the even more detailed regulation of the medicinal products, that is why the Directive was amended step by step in the majority of the aspects, providing new grounds and finally the specific new regulation was introduced in 2011.
3. According to the new European Union prevention regulation of the entry into legal supply chain of falsified medicinal products, all EU member states are obliged to bring their own legislation and trade practices in line with the requirements of this directive until February 9, 2019. It is important to note, while the updated requirements implied that protection against the falsification of the medicinal products is carried out by applying a special unique number on the packaging, which will allow to distinguish falsified medicinal products from the original ones, since the unique number of each package can be checked at any time using a special database on the European and national levels.
4. Falsified medicinal products have to be quickly detected and removed from traffic without incident. Manufacturers who do not have such a tracking solution will have to withdraw their products from the European market. The tightening of regulations, dictated by the fight against falsification of medicinal products, requires measures of maximum security throughout the supply chain in the manufactures of pharmaceutical products that is beneficial for the patients, while each participant in the supply chain can provide information about the origin of the medicinal product and its further movement. Thus, producers and distributors must themselves control and identify to whom they supply and from whom they purchase products throughout the entire chain.

[RQ2]: What are the updated or newly created duties of the pharmaceutical products distributors?

5. The EU Directive No. 2011/62/EC introduced new obligations for wholesalers, which concern standards in the quality system, personnel training and hygiene, facilities and equipment, documentation, thus updating the Good Distribution Practice. There are new requirements for the equipment, especially computerised systems - the validation or verification of all systems that are proving that the

system is capable to achieve the necessary results is required, with all the tests included.

6. The companies should also provide a document which has to state all computer systems used within a company and describe the principles and features of interaction between these computer systems. Moreover, the hardware and equipment should also be validated and in case if any maintenance or change occur, the new validation and new tests should be performed, after which the new document has to be presented.
7. All the products should be checked via the national database, where the producer of the product has to upload the information about each package produced. When arriving to the wholesaler, the batch of the medicine has to be verified in order to avoid the potentially falsified products in case when medicinal products arrived directly from the producer.
8. All the records of verification and the potential threats if any have to be stored. In case of the product recall from the market, if product is returned or suspected - the wholesalers in the whole distribution chain have to verify (scan) each package of the product again. Distributors and representatives of the producers are also responsible for marking a package if the product is quarantined, removed from sales as a sample for testing, and other similar activities. Implementation of this system in Latvia required a radical improvement in the IT infrastructure (computers and Internet access points) which resulted in substantial financial costs for manufacturers (installation of additional equipment, modernization of packaging lines, installation of track & trace systems), distributors and pharmacy chains (software, scanners, staff training).
9. In order to provide the compliance with the legal requirements, medicines are scanned individually or in a bulk with the business application in single transaction process verification. In order to comply with the renewed GDP requirements and new requirements set by Directive on the prevention of the falsified medicinal products, the companies had to update all the standard operations and other documents. All the documents were formed according to the international and national norms.

[RQ3]: What are the conflicts and problems pharmaceutical products distributors face while implementing the new requirements set by the updated regulation?

10. Distributors face the failure of the EU hubs performance, while in the first month when the regulation came in force, the European Union IT infrastructure was detected as not ready to perform correctly with given number of transactions and users.
11. Distributors face the technical impossibility of applying an individual code. It was a problem for the number of producers to apply the code to existing packaging due to its small size or inappropriate shape. This resulted in the wrong placement and disability of the distributor to scan the package in an ordinary way.
12. Distributors face the scanning failures. This issue was claimed to be the most serious and risky and is investigated by the national and EU agencies. Some of the uploaded data by the producers is not correctly represented on the international and/or national data storage levels. This occurs due to the lack of several features, that in some repositories are mandatory, but in others - are not, as well as due to the technical misclicks and similar issues. These cases are consequent and are

repeating almost every week, urging the distributors to move the packages to the quarantine area and not being able either to return, or to sell the medicinal products, even despite the fact that the medicinal products are not falsified, are approved by laboratory, and even in case of the reimbursed medicines or medicines for the hospitals, that are urgently needed for patients in critical conditions.

13. Distributors are obliged to invest in the new equipment, training, as well as connection to the national databases, that is hardly covered by the income of the companies, while the majority of the medicines are sold directly to the state institutions with the loss or with the wholesalers controlling the pharmacy chains with the minimal mark-up, while the prescription medicines mark-up is managed and set up by the national regulations. It means that the company will face the necessity to cover the expenses by the changes in the OTC medicinal products' prices introducing the financial pressure on producers, distributors and end users.
14. Incorrect or incorrectly functioning systems of validation of medicinal products lead to the fact that distributors or manufacturers are not able to deliver to the market those products which are not validated by the new system. Consequently, medicinal products for patients from the reimbursement list are not available in a timely manner, and similar ones are available for money; secondly, medicinal products for hospitals, prisons and other social and state institutions responsible for treating the population are not available in a timely manner; thirdly, medicinal products are not available, which should be delivered on time according to the public procurement contracts. In such a situation, a violation of a number of patients' rights occurs, as well as a conflict of interests and restriction of the distributor's freedom. In this case, the basic rights of the patient are violated, while the patient cannot choose the therapy or medicinal product, cannot choose the treatment, he faces the limited choice. Moreover, the patient cannot claim reimbursement in the required amount, he is obliged to invest personal financial resources in order to continue therapy, and in case of a shortage of financial resources his right to access health care is limited. Similarly, the social rights of patients who are admitted to hospitals, where there are no medications to be provided by the state, are limited. Finally, the patient has to choose the provider of the therapy, who is able to provide the medicinal product, while the access to the medicinal products are not equal. The patient cannot choose the pharmacy, while in case of the computer failures, he has to choose the pharmacy with the more updated technical support, otherwise the medicinal products cannot be dispensed.
15. Distributors face a conflict of interest between the manufacturer, state buyers, distributors and patients. Medical institutions that have concluded a contract with distributors have the opportunity to claim compensation or a fine if the goods are not delivered. In turn, when the verification system fails, the distributor does not have the right to make deliveries, but this happens not through his fault, but because of failures in the international information system. Accordingly, a situation arises that the distributor may incur losses, the hospital incurs losses and does not fulfil obligations to patients, and the rights of patients are limited. Such situations impose an additional financial burden on the distributor, together with losses and a heightened profit, which he/she incurs because of the impossibility of selling good.

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