UNIVERSITY OF LATVIA

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IMPACT OF LEGISLATIVE CHANGES ON THE AVAILABILITY OF MEDICINES AND PHARMACOVIGILANCE ACTIVITIES

DOCTORAL THESIS

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ANOTĀCIJA

Zāļu normatīvā regulējuma izmaiņu ietekme uz to pieejamību un farmakovigilances aktivitātēm

Zāļu pieejamība ir vispārējas cilvēktiesības, tomēr tā joprojām saglabājas globāla problēma. Šajā pētījumā par objektu izvēlēts Latvijas lielākās kaimiņvalsts – Krievijas Federācijas (KF) – zāļu normatīvais regulējums, kurā 2010. gadā notika radikālas izmaiņas, kas noveda pie papildu administratīvā sloga un ietekmes uz zāļu pieejamību un farmakovigilances aktivitātēm. Tā kā Latvijas farmaceitiskajiem uzņēmumiem un citu Eiropas Savienības (ES) valstu zāļu ražotājiem KF tirgus ir nozīmīgs, tiem būtu noderīgi iegūt zinātnisku ieskatu zāļu reģistrāciju regulējošos procesos kas palīdzētu uzlabot to darbību. Pētījums ir nozīmīgs arī valsts iestāžu darbiniekiem, lai paredzētu sekas un plānotu normatīvo aktu izdošanas procesu.

Līdz tiesību aktu izmaiņai KF centās ņemt vērā pasaulē atzītu Amerikas Savienoto Valstu (ASV) un Eiropas zāļu normatīvo regulējumu. Savukārt pēc jaunā zāļu likuma ieviešanas 2010. gadā tika izveidota unikāla regulatīva sistēma, kas neatbilda ne ASV, ne Eiropas praksei. Šī pētījuma laikā pirmo reizi normatīvā regulējuma efektivitāte tika statistiski novērtēta, un ietekmējošie faktori tika kontrolēti, pamatojoties uz reģistrēto zāļu skaitu un farmakovigilances ziņošanas aktivitātēm. Pirms jaunā zāļu likuma Krievijā bija reģistrēti 20 836 medikamenti un 5000 uztura bagātinātāji. Pēc jaunā zāļu likuma – 16 409 medikamenti pret 9500 uztura bagātinātājiem. Kritums bija -21,25%. Turklāt pirms jaunā zāļu likuma 2008. gadā izsniegto zāļu reģistrācijas apliecību skaits bija 3043, bet divus gadus pēc izmaiņām 2012. gadā tikai 1092. Atšķirība bija -1975 apliecības gadā, un atšķirība atšķirībās, pieņemot uztura bagātinātāju tendenci, bija -1978. Kritums bija diezgan acīmredzams: -64,11%. Ziņotās zāļu blakusparādības pirms jaunā zāļu likuma 2008. gadā Krievijā bija 0,042 uz 1000 iedzīvotājiem, savukārt divus gadus pēc izmaiņām 2012. gadā – jau 0,120. Atšķirība bija 0,079 ziņojumi gadā. Salīdzinājumā ar ES KF tendence bija negatīva: -1,224 ziņojumi, tomēr ziņošanas aktivitātes Krievijā 2012. gadā palielinājās par 185,71%, savukārt ES tikai par 117,51%.

Secinājumi. Neskatoties uz nodomu sinhronizēt zāļu normatīvo regulējumu ar labāko starptautisko praksi, KF joprojām ir savas īpatnības, kurām nav līdzīgu. Jaunā zāļu likuma un no tā izrietošo administratīvo reformu veikšana novērojamā periodā samazināja piekļuvi zālēm. Pretēji tam zāļu drošuma uzraudzības sistēma guva panākumus, un to nodrošināja starptautiskas pieejas ieviešana, nepakļaujot atbildīgās iestādes būtiskām administratīvām reformām.

ANNOTATION

Impact of legislative changes on the availability of medicines and pharmacovigilance activities

Access to medicine is a universal human right; however, it is still a global problem. In the present study, we chose the regulatory system of drug registration of the largest Latvia neighbouring country, the Russian Federation (RF), as the object of research, which in 2010, underwent radical changes leading to regulatory pathway burden; these changes impacted the availability of drugs and pharmacovigilance activities. As of now, there are pharmaceutical manufacturers from Latvia and other European Union (EU) countries that have important markets in the RF; it would be helpful for them to have a scientific insight into the regulatory processes and enhance their medicines registration process. The study is also important for state decision makers to plan changes and predict their potential impact.

Until the change in legislation, the RF tried to follow the world-recognized guidelines of the United States (US) and European drug registration legislation. In turn, after the introduction of the new pharmaceutical law (NPL) in 2010, a unique legal system was created that did not correspond to either the US or the European practice. In this study, for the first time, legislation performance has been statistically evaluated and study confounders controlled based on the number of authorized medicines and pharmacovigilance reporting activities. Before the NPL, 20836 drugs and 5000 food supplements (FS) were registered. After NPL, 16,409 drugs in the State Medicines Register vs. 9500 FS were noted. The fall was −21.25%. Additionally, before the NPL, in 2008, drug MAs issued per year were 3043, whereas the number was 1092, two years post intervention in 2012. The difference was −1975 MAs/year and difference-in-differences, assuming the FS trend of 1978. The fall was obvious at −64.11%. The reported adverse drug reactions before the NPL, in 2008, were 0.042 per 1000 inhabitants, whereas two years post-intervention of the NPL, in 2012, the number reported was already 0.120. The difference was 0.079 reports/year. Although differences-in-differences, assuming the EU trend, still showed negative performance at −1.224 reports, the increase recorded in the reporting activity in Russia in 2012 was 185.71%, whereas in the EU it was 117.51%.

Conclusion. Despite the intention of synchronizing the marketing authorization system with the best international practices, the RF still has its own peculiarities. The implementation of the NPL and consequential administrative reforms during the observational period led to reduced access to medicines. In contrast, the drug safety monitoring system succeeded, which was ensured by the implementation of an international approach and the system not being exposed to administrative turmoil.

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ABBREVIATIONS

AC – accreditation certificate

ACTO – Association of Clinical Trials organisations

AD – adverse reaction

ADR – adverse drug reactions

AIS – Automated Information System of Roszdravnadzor

APP – Authorized Person of Pharmacovigilance

CA – competent authorities

CB – Certified Body

CEU – Court of the Eurasian Economic Union

CHEP – Centre for Hygienic Education of the Population

CT – clinical trials

CTD – Common Technical Document

CTCB – Certification and training centre for biocorrectors

CU – Commission of the Customs Union

DiD – Differences-in-Differences

EAEU – Eurasian Economic Union

EC – European Commission

EFSA – European Food Safety Authority

EMA – European Medicines Agency

EU – European Union

EUEC – Eurasian Economic Commission

EUGVP – good pharmacovigilance practice of Eurasian Economic Union

EUIC – Eurasian Intergovernmental Council

EEUPC – Eurasian Economic Union Pharmacopoeia Committee

FCMSM – Federal Centre for Monitoring the Safety of Medicines

FDA – Food and Drug Administration

FGU – Scientific Centre for Expertise of Medical Products

FS – food supplements

GMP – Good Manufacturing Practices

GOST – set of technical standards

GVP – good pharmacovigilance practices

ICH – International Council on Harmonization

MA – marketing authorization

MAH – Marketing Authorization Holder

MCA – Agreement on common principles and rules of circulation of medicines within the framework of the Eurasian Economic Union

MedDRA – Medical Dictionary for Regulatory Activities

MHSD – Ministry of Health and Social Development of Russian Federation

MOH – Ministry of Health

MS – Member States

NCE – Nowel Chemical Entities

NCO – non-commercial organizations

ND – normative documentation

NPL – new Pharmaceutical Law

OST – Standards and Standards of the Industry

OL – old law

PSUR – Periodic Safety Update Report

PV – pharmacovigilance

RF – Russian Federation

Rosakkreditatsiya – Federal Service for Accreditation

Roszdravnadzor – The Federal Service on surveillance in healthcare and the social development of Russian Federation

SAE – serious adverse reactions

SC – Supreme Eurasian Economic Council

SE – side effects

SmPC – Summary of Product Characteristics

SMR – state register of medicines

SR – safety reporting

SUTVA – Stable Unit Treatment Value Assumption

TRCU – Certification System on Technical Regulations of the Customs Union

TU – Treaty on the Eurasian Economic Union

UR – unified register

US – United States

VC – voluntary certification

VCC – voluntary certificate of conformity

VCS – voluntary certification system

WG – Working Group

WHO – World Health Organization

WTO – World Trade Organisation

YC – Yellow card

1. Introduction

Access to medicines is a universal human right; however, it is still a global problem (Rathish *et al.*, 2017). Pharmaceutical use and accessibility are also important indicators of population health, as they play a role in maintaining health, reducing global morbidity and mortality. The experience of the European Union has shown some success in drug regulation (Tiguman, Silva and Galvão, 2020).

Most health system improvement interventions ignore the relationships between system components. In particular, the complex relationship between medicine and service delivery, health financing, human resources, and medical information does not receive enough attention. As a result, public access to medicines is mainly addressed through fragmented, often vertical approaches, usually with a focus on supplies, that are not related to the broader issue of access to health services and interventions (Bigdeli *et al.*, 2013).

As mentioned in the World Health Organization report (WHO, 2004), most countries have drug regulatory authorities and formal requirements for drug registration. However, drug regulatory authorities vary significantly in their human and financial resources and overall effectiveness. Less than one in six WHO Member States has a well-developed drug regulation system, and two out of six Member States do not have or have very limited drug regulatory potential. In addition, the quality of drugs varies greatly, especially in low-income countries, and regulatory gaps are common in the production and distribution sector.

In regulatory practice, three types of general imbalance–excessive concentration on pre-sale and not on post-market monitoring (pharmacovigilance; PV), increased attention on registration and less on the distribution system, and more intensive production site evaluation than distribution channels have been identified (WHO, 2004). These findings help the national registration authorities to fulfil their duties in an effective, efficient, predictable, and transparent manner, and is therefore of critical importance to ensure the quality, safety, and efficacy of health products in an increasingly complex global environment (WHO, 2020). Despite the complexity of this issue, the concept of strengthening national and regional regulatory systems as the foundation to ensure timely access to quality medicines is often not given due attention (Karrar, 2019).

The Russian pharmaceutical market was very dynamic and growing at the start of the 21st century. Though the volume of the Russian pharmaceutical market in 2018 reached 1.682 trillion rubles exceeding expectations according to the Concept of Long-Term Socio-Economic Development (Прав. Рос. Федерации, 2008), which was 2.6% higher than the

volume reported a year earlier. However, the exchange rate for the ruble was 44.2 RUR/1 EUR in 2009 (Ratestats.com, 2009) vs. 74.1 RUR/1 EUR in 2018 (Ratestats.com, 2018). The sales volume of drugs in packs increased by 1.5% and amounted to 6.4 billion packs (Шуляк *et al.*, 2018).

The Federal Law introduced in 1998 regulated the procedure of marketing authorization (MA) on medicines. Some other acts describe the standards in the technical processes of obtaining MA. However, it was its own unique regulatory system, which did not completely comply with the U.S. or European practices, but used its own general principles.

The acting regulatory authority was the Scientific Centre for Expertise of Medical Products. Approximately thirty officers were performing daily activities. However, the dossier evaluation was outsourced to different subcontractors called non-commercial organizations, which substantially decreased the Scientific Centre's workload, dossiers evaluation time, and quantity. Despite a lack of detailed procedural description of drug registration requirements in the legislation, the system of MAs in the Russian Federation (RF) performed satisfactorily until the introduction of new pharmaceutical law (NPL). The Scientific Centre for Expertise of Medical Products compensated for the legislation's deficiencies by issuing letters and recommendations though they were not easily accessible for the public. These documents contained detailed procedural descriptions and dossier requirements. Clinical trials were required for novel chemical entities (NCE).

Generally, no national clinical trials were mandatory for generics, and overall, the existing MA scheme was mostly in accordance with international practices.

With declared intention to increase the availability of good quality, safe, and clinically-effective drugs for the citizens, the State healthcare stakeholders announced strategies for developing the pharmaceutical industry of the RF until 2020 (Прав. Рос. Федерации, 2008). One of the strategies was to improve the system for assessing the quality of the medicines and eliminating excessive administrative barriers to the MAs of domestic drugs and bring Russian pharmaceutical standards in line with the international to increase the competitiveness of the national pharmaceutical industry. In the light of strategy 2020 (Прав. Рос. Федерации, 2008) the Ministry of Health and Social Development revealed some deficiencies of the existing MA system and issued the draft law, "On Circulation of Medicines." Despite public criticism, the Ministry was convinced that the draft would resolve some existing issues such as unfair competition between domestic and foreign pharmaceutical manufacturers. The Ministry also noted that the existing MA procedure lacks transparency, as there were too many institutions involved in the dossier evaluation process, and a single authority is missing. It also stated that the MA duration is very long and expensive; therefore,

a single and complete state fee for the MA is necessary. Thus, any additional fees would be eliminated and prohibited. The Ministry expected that the definition of the maximum MA issue term of 210 days would definitely lead to a decrease in registration process time. The unique invention introduced by the draft was the requirement of local clinical trials for almost any even generic medicine. Interestingly, clinical trials were initiated before the quality and safety testing of the drugs.

The NPL was finally introduced in the middle of 2010, resulting in seven amendments within three years. Authorities issuing MA were reorganized and resubordinated. A new specialist staff member was employed, and the MA issue time greatly exceeded 210 days. After 2010, a unique authorization system, for which there were no analogies internationally, was established in the RF. Despite declared improvements, the MA system experienced a lack of transparency concerning the procedures leading to frequent amendments. An attempt to link the best international practices nationally was made by the introduction of common Eurasian Economic Union legislation related to medicines, though that system is still not operational.

The present research investigates and analyses the pharmaceutical regulatory legislation environment and its performance after the introduction of the NPL in the RF in 2010. This is the first time legislation performance has been statistically evaluated based on the number of authorized medicines and PV reporting activities. The study confounders were controlled by using differences-in-differences (DiD) estimation comparing NPL (Федеральный закон, 2010) to similar food supplements (FS) legislation in the RF. In the DiD estimation related to PV reporting, a comparison with European Union performance was evaluated.

Novelty of the study

This was the first study in which drug regulatory changes due to the introduction of new Pharmaceutical Law in the Russian Federation in 2010 were analysed. The legislation was assessed using qualitative research based on descriptive analysis of legal acts and regulatory policy before and after NPL introduction. The quantitative research was performed by statistical evaluation controlling confounders. The analysis of this unique situation and consequences will be useful for process modelling and anticipation of the development options of planned legislative changes, their possible influence on the efficiency of the responsible institutions as well as the impact on availability, and safety of medicines.

Aim of the study

The research conducted in the study aimed to perform a comprehensive critical review of legislation changes and their impact on society's health in terms of access to medicines as well as PV activities in the RF during the period from 2008 until 2017.

The questions of the study were the following:

1) How did the regulatory environment change after the introduction of NPL?
2) What was the impact of NPL on access to medicines?
3) What was the impact of NPL on the drug safety reporting system in the RF?

Objectives of the study

The objectives of the present research were as follows:

1) Analysis of the regulatory framework governing the scope of dossier examination of medicines during their state registration and PV activities in the RF from 2008 to 2017.
2) Assessment of the impact of NPL legislation on the overall number of registered drugs and issued medicine MA per year employing difference-in-differences statistical approach by comparing similar legislative environment of food supplement registration in RF at two different times, 2008 and 2012.
3) Evaluation of the impact of NPL legislation on PV reporting activity in RF employing a difference-in-differences statistical approach by comparing similar legislative environment of EU at two different times, 2009 and 2012.

Hypotheses of the study

H1. The additional regulatory and legislative constraints after the introduction of the NPL led to differences in medicine registration procedures between the RF and well-recognized international practices.

H2. NPL's performance led to decreased drug accessibility by reducing the number of registered medicines and the MAs issued per year.

H3. The performance of NPL regarding PV reporting is acceptable compared to the EU.

2. Literature review

2.1. The key burdens limiting medicines access in the world

Access to quality medical products improves health and saves life. However, one-third of the world's population experiences a shortage of timely access to quality medicines, whereas estimates indicate that at least 10% of medicine in low- and middle-income countries are substandard or adulterated, costing approximately 31 billion US dollars annually (Roth *et al.*, 2018).

High medicinal product prices, low affordability, and reduced availability are known as crucial obstacles limiting access to adequate treatment in many low- and middle-income countries. Indeed, in countries where most of the population still buys its pharmaceuticals through means of monetary payments, the high cost of medicines (relative to the family budget) means that morbidity in the family exposes these people to the risk of enormous expenditure. Very often, the choice is to avoid the use of necessary medicines. Inequality in access to medicinal products is widely perceived as a distinct weakness in the healthcare system. It represents a failure on the part of national governments to comply with their obligations toward their nations in terms of their right to health.

Ensuring equitable access to quality pharmaceuticals is thus a crucial development difficulty and an essential component of health system conditioning and primary health care reform programs throughout international society.

The Millennium Development Goals issued by WHO acknowledges the critical importance of improving access to medicines as target 8E, which assumes cooperation with the pharma industry, to provide access to affordable essential drugs in developing countries. Improved access is also named as a prerequisite to the achievement of several other development goals, such as reduction of child mortality, improvement of maternal health and fighting against HIV/AIDS, malaria etc. (WHO, 2011).

The 2011 data reveals that in all regions, public sector availability of generic medicines is, on average, less than 60%, ranging from 32% in the Eastern Mediterranean to 58% in Europe. However, an apparent alteration was observed across the individual countries of all regions; the most substantial differences between the lowest and highest median availability are seen in the Eastern Mediterranean and Europe, and the smallest in both Americas and South-East Asia (WHO, 2011).

The availability of originator brands in the public sector is low, with most governments favouring the purchase and distribution of lower-priced generic equivalents.

Countries with the highest public sector availability of originator brand products were Kuwait (12.0%), the Islamic Republic of Iran (13.3%), the United Arab Emirates (16.7%), and Ukraine (50.0%).

In contrast, availability of generic medicines in the private sector was more significant than that in the public sector in all regions. Nevertheless, median availability was still less than 60% in Africa, Southeast Asia, and the Western Pacific. Large differences in availability across individual countries within the same region were again observed; the difference between the least and most availability was 98% and 74% in the countries of the Eastern Mediterranean and Africa, respectively. Elsewhere, particularly in Europe and the Americas, the range in availability was much smaller (21% and 27%, respectively). It was concluded that this might be due, at least in part, to the smaller number of participating countries in these regions (only six in each area). The availability of originator brands in the private sector was consistently lower than that of generics in all regions. The availability of these products was less than 25% in all regions, with the exception of the Eastern Mediterranean, where the average private sector availability of originator brands is notably higher (58%) but with a wide range across individual countries (median availability ranges from 0% in the Sudan and Syrian Arab Republic to 100% in the United Arab Emirates) (WHO, 2011).

Regarding the pricing of medicines in many countries, pharmaceuticals are provided free to all patients in the public sector. However, in this case, price data are not reported. In countries where medicines are only provided free to some groups of patients (e.g., children, the elderly, and others), data on the price paid by those who are required to pay for their medicines were collected. In such cases, the price reported is the full price paid, even if patients pay only part of this price. In some countries observed by the WHO in 2011, in which patients were required to purchase drugs in the public sector, prices paid for the lowest-priced generic medicines, on average, ranged from 1.9 times the international reference price in the Eastern Mediterranean to 3.7 times the International Reference Pricing in Europe. In post-Soviet countries such as Ukraine, Kazakhstan, high procurement prices (3.5, 3.0, and 5.1 times the international reference price, respectively) were largely responsible for the high patient prices in the public sector.

Although the availability of originator medicines in the public sector was generally low, when such products were sold to end users, prices tended to be very high. The average prices with respect to the international reference price ranged from 5.3 times in the Eastern Mediterranean to 20.5 times in Europe (WHO, 2011).

The low availability of medicines forced patients to purchase medicines from the private sector, often at prices they can weakly afford. The WHO survey revealed that the

prices of medicinal product– particularly those of generics – are higher in the private sector. In the case of generic products, two distinct patterns emerge across the world. Among the countries surveyed, moderately high median price ratios were observed in Europe, Southeast Asia, and the Western Pacific, with only small variations across the individual countries in each region. Although the observed variation among neighbouring countries was small, variation across individual medicinal products within a country was substantial.

Affordability of purchasing treatment in the private sector, the third drug access-limiting factor in the private sector reflected the significant differences in both originator brand products and lowest-priced generics that exist in many countries. It was revealed that even when lower-priced generic medicines are available, treatment is beyond the reach of many citizens in low- and middle-income countries. For example, the treatment of respiratory infections with generic ciprofloxacin cost over a day's wage in nearly all countries. The exception among post-Soviet countries was that of Ukraine (0.7 day's wage). Treatment with generics accounted for over two days' wages in over half of the countries studied by WHO. The position was far worse when the originator brands were considered. The treatment with the originator drug would cost the lowest-paid government worker over 10 days' wages in over half of the countries studied. Nowhere did treatment with a branded medicine cost less than 2 days' wages. Therefore, treatment was described as continually unaffordable not only for the lowest-paid employees, but also for the majority of citizens earning less than average (WHO, 2011).

State MA of medicines is dedicated to guarantee the availability of therapeutically-effective, safe, and high-quality drugs for the population. The availability depends on the number of authorized pharmaceuticals in the market.

2.2. Reduced availability of medicines in the world

The WHO survey of 2011 concluded that among several contributing causes concerning the inadequate availability of medicines, a single regulatory policy response is unlikely to be sufficient. To affect real change and maximize impact, a comprehensive package of policy reforms that is implemented fully and rigorously enforced, is usually required. Therefore, monitoring the effects of policy reforms is vital, especially as all policies can have unintended consequences. For example, processes that set prices too low can frustrate the manufacturing and warehousing of a medicinal product, whereas setting maximum wholesale and retail margins can provide compulsory incentive for turnover chain operators to carry those higher-priced medicines that will gain greater profits (WHO, 2011).

It was suggested that there are abundant opportunities to increase drug availability, lower prices, and improve affordability of medicines in all regions and at all levels of economic development.

Despite some verified successes, many countries are still failing to implement the policy and action plans necessary to improve access to affordable medicines. Although the challenges faced differ among countries, the general problem is a lack of technical capacity to link price data to local policy processes and to identify and prepare suitable responses. A related issue is the scantiness of published evidence on the effectiveness of different regulatory approaches in low- and middle-income countries. Moreover, the lack of political allegiance due to conflicting industrial or trade policies can act as a barrier to the adoption of actions aimed at reducing medicine prices and improving availability in both public and private sectors (WHO, 2011).

Thus, the medicines policy, assuming a deliberate system of legal principles to guide decisions and achieve rational outcomes, plays a crucial role in ensuring the availability of medicines.

2.3. Objectives of Pharmaceutical regulation

Pharmaceutical regulation is a government policy that restricts the activities of the private sector to achieve the social goals set by the state (WHO, 2002).

However, any practice of regulatory evaluation should initially clarify the key definitions and concepts behind that activity. As discussed in the literature, the term regulation itself can mean various things. At the basic level, regulation is synonymous with law. Regulations are rules or norms adopted by governments and argued by some hazardous consequences, usually negative ones in the form of penalties. Often directed at particular businesses such as the pharmaceutical industry, regulations can also aim for non-profit organizations, other governmental entities, and even citizens. Given their variety, regulations can be described differently, regardless of the purpose of evaluation. The most important is that evaluators are precise regarding exactly what they seek to evaluate; however, that institutional action may be labelled by other players differently (Coglianese, 2012).

The regulations of medicinal products are a combination of all measures – legal, administrative, and technical – that governments take to ensure the safety, effectiveness, and quality of drugs, and the relevance of product information (WHO, 2002). In the modern view, the most recent knowledge of science enhances the development of pharmaceutical

regulations. There are two significant issues forcing governments to intervene in the medicines sector, namely public health and drug safety (WHO, 2002).

Although pharmaceutical regulation is mainly a state function, regulatory activities can also be carried out by private organizations, if they have received permission from the agency, whose own powers are provided by law. Equally, a government can decide to apply the same regulatory requirements for public facilities as it does for the private sector. For example, good manufacturing practices (GMP) standards may apply to both state and private producers. Self-regulation also occurs in which members of a legally oriented group organize, among themselves, and have some means of mutual control.

Ensuring the safety, efficacy, and quality of medicines available to the public are the primary goals of pharmaceutical regulation, which cover many functions. Key features include licensing of premises, individuals, and practices; verification of production capacities and distribution channels; product evaluation and registration or MA; PV (monitoring adverse drug reactions (ADR)); quality check; control of medicine promotion and advertising. Each of these functions focuses on various aspects of pharmaceutical activity, but all of them must be performed simultaneously to ensure effective consumer protection (WHO, 2002).

Given that pharmaceutical legislation requires the state to use public resources to impose restrictions on private business, several regulatory issues arise: for example, is the regulation of certain activities justified; what restrictions should be applied and to what extent; the level of resources used to fund state interventions and their source; the effectiveness of legal functions; who is responsible for the positive and negative effects of regulatory actions.

The missions and goals set by any state form the background for its decisions to interfere with the chosen activities of the society. Therefore, it is necessary to define the objectives of pharmaceutical regulation. Most of the countries reviewed stated that the primary objective of national medicine regulation is to ensure the safety, efficacy, and quality of medicines available to the public.

In addition, the Federal Law of the RF No. 61-FZ "On Circulation of Medicines"' establishes the priority of state regulation towards ensuring the safety, quality, and effectiveness of medicines in circulation.

2.4. Pharmacovigilance

According to the WHO, PV, also known as the 'safety of medicines,' is the science and activity involved in identifying, assessing, and preventing side effects. The purpose and

scope of PV are broad and include several components, such as drug use errors, adulterated and unauthorized medicines, inefficiencies, drug interactions, and rational prescribing (WHO, 2020).

The WHO defines adverse drug reactions as "any adverse and unintended drug reaction that may occur in doses used particular medicine for prevention, diagnosis, or treatment." Worldwide, the high prevalence of ADR has increased morbidity and mortality in both hospitals and society. ADR is known to be among of the leading causes that are harmful to patients worldwide. In many countries, ADR is the leading cause of mortality and morbidity (Najafi, 2018).

The PV, as defined by the European Commission (EC), is the process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines. The international PV systems aim to monitor the risk/benefit ratio of drugs as well as improve patient safety and quality of life. PV activities include collecting and managing data on the safety of medicines, looking at individual case reports to detect new "signals," pro-active risk management to minimize any potential risk associated with the use of medicines, and communicating and informing stakeholders and patients. This seamless post-marketing surveillance, which is primarily aimed at protecting the public, allows controlling authorities to modify – on the basis of newly discovered signals – the Summary of Product Characteristics (SmPC), released by the marketing authorization holder (MAH) for any new medicinal product at the first boot into the market (European Medicines Agency, 2017c).

Improving public health and accurate assessment and monitoring of drug safety are critical to preventing or reducing patient risk in any country. An effective reporting system for PV and adverse reactions must be established throughout the world to achieve that aim. Worldwide PV system development started after the thalidomide disaster in the 1960s, when thousands of babies were born with phocomelia as a side effect of thalidomide, resulting in shortened or missing limbs. Thalidomide was a widely used drug in the late 1950s and the early 1960s to treat nausea in pregnant women. In the 1960s, it became clear that treatment with thalidomide causes serious birth defects in thousands of children. However, thalidomide was banned in most countries at that time, despite its usefulness in treating leprosy and, later, multiple myeloma.

The tragedy of thalidomide raised many questions on drug safety and questioned the creation of systems to evaluate and ensure drug safety in all countries.

The cost of mortality and the incidence of diseases are much higher than the price of the drug development process itself. On average, 10 % of authorized pharmaceuticals are

withdrawn from the market due to serious side effects. Pharmaceutical companies spend approximately a billion dollars on a single drug development, which can take many years. Although a significant amount of information on the effectiveness of the medicines could be obtained during the development of a pharmaceutical product, it is not possible to establish a complete product safety profile in preliminary marketing research. However, some drugs may have been withdrawn from the market due to safety concerns associated with serious adverse events (Najafi, 2018).

The worldwide ban of the novel non-steroidal anti-inflammatory drug rofecoxib (Vioxx) in 2004 has played an essential role in implementing new safety reforms at the United States (US) Food and Drug Administration (FDA) rule making. Initially, it was believed that rofecoxib which was approved by the FDA in 1999, would be safer than previous painkillers because it had a lower risk of bleeding from the gastrointestinal tract. However, it has been estimated that this medicine has led to fatal heart attacks in 160,000 patients in the United States.

As noted by FDA leading office Dr David J. Graham, rofecoxib story may be the single greatest drug safety catastrophe in the history of United States or the history of the world (Graham, 2004).

Regarding recall, there has been widespread debate on US FDA safety procedures reforms before and after the marketing of medicines. It is also important that healthcare providers and pharmaceutical companies properly monitor the safety of drugs during the post-approval phase.

Pre-MA clinical trials do not address all safety concerns. The disadvantages of clinical trials to determine the safety of a drug are the small sample size of the study, limited age groups (excluding children, adolescents, the elderly, etc.), the short duration of the study, and restrictive specific indications. After the appearance of drugs on the pharmaceutical market, they are exposed to mass groups around the world. In addition, information on adverse reactions is collected over time, as drugs is used for several indications or in different subgroups of patients, and this restriction changes the safety profile of the drug. Therefore, when medicines have recently appeared on the market, much can be known regarding their effectiveness, and relatively little regarding their safety. Post-marketing surveillance is vital for identifying drug safety issues that were not identified during pre-sale research. After this, the primary source of safety information for newly approved drugs is the post-marketing surveillance of adverse reactions in both the population and the clinic.

In Europe, milestones of the development of PV systems are shown in Figure 2.1.

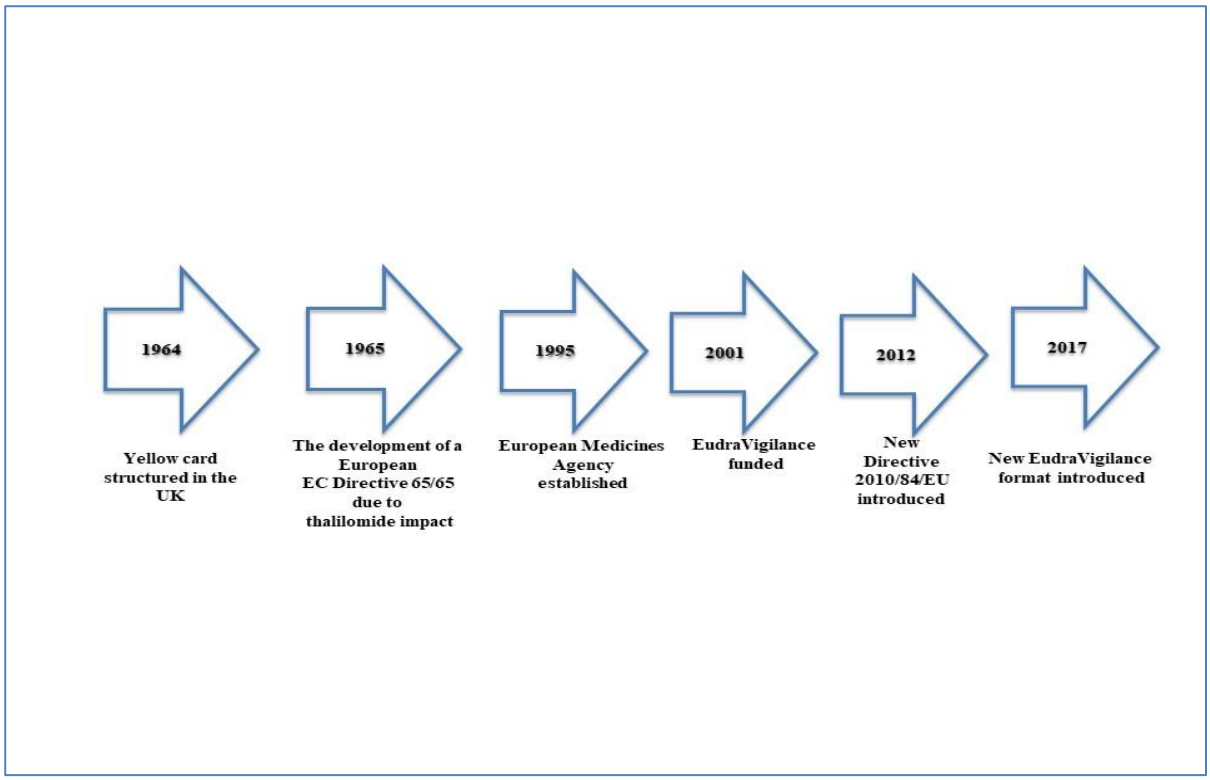


Figure 2.1. The development of PV system in the European Union

In 1964, the "Yellow card" (YC) was developed in the UK. YC is a specific form that compiles a spontaneous report of drug toxicity.

After the disaster of thalidomide, the development of European legislation with the EC, Directive 65/65 was promoted. Further, in 1995, the European Medicines Agency (EMA) was established. In 2001, EudraVigilance (Eudra Vigilance, 2020), which is the official European database for managing and analysing information on suspected adverse reactions to medicines that have been authorized for the market or being studied in European clinical trials, was funded. A significant change in the European Pharmacovigilance was observed with the new legislation Directive 2010/84/EU (The European Parliament and The Council, 2010), in 2012. The main changes in the new legislation assumed the following:

- modification of the definition ADR;
- greater involvement of the whole society in PV activities;
- strengthening of the EudraVigilance database containing reports of suspected reactions reported by all EU member states.
- increasing transparency and timeliness of important information on PV problems;
- obligation of additional monitoring for the medicines contained in the specific list kept by the EMA;
- possibility to continuously impose safety and/or efficacy studies on the certificates of MA at the time of granting the trust;

- establishment within the EMA of the Pharmacovigilance Risk Assessment Committee (PRAC) (Fornasier *et al.*, 2018);
- establishment within the EMA of the Pharmacovigilance Risk Assessment Committee (PRAC) (Fornasier *et al.*, 2018).

As the latest development in November 2017, the new EudraVigilance format was launched, where the MAHs will have extended access to the EudraVigilance database to support the fulfilment of their PV liabilities. These obligations include the continuous monitoring of EudraVigilance data and the communication of validated signals to the Agency and national regulatory authorities, as outlined in the Commission Implementing Regulation (EU N. 520/2012) (European Commission, 2012).

In summary, knowledge and perception by health professionals of the drug safety profile is crucial for any healthcare system. Medical practitioners should be aware of the possibility of ADRs and report them to regulatory authorities to facilitate the detection and evaluation of safety signals. In addition, they should be mindful that none of the pharmaceuticals is entirely safe for everyone, anywhere, and anytime. Therefore, the regulatory empowerment of the PV process is the keystone of any pharmaceutical legislation and should be scrutinized to avoid implementation consequences.

2.5. National pharmaceutical regulatory policies

Medicines markets are both multifactorial and crucial and require careful management.

Pharmaceuticals are essential for the economy of the country and the health of its inhabitants, but these two interests may conflict. National laws and regulations relating to medicine are often inconsistent and incomplete, and without an integrated framework, there can be worry regarding the general health policy objectives. Precise medicine policies supported by trust authorities can ensure that all stakeholders are aware of their roles, rights, and obligations and that they are supported by monitoring and effective regulations (WHO, 2004).

WHO guidelines for national drug policies describe the policy development process and the necessary accompanying legislation and define critical components of expected national policy. Formally, the guidelines reflect the decisions, goals, and commitments of the government and other people.

National drug policy defines national objectives and provides the basis for the achievements, outlining the roles and responsibilities of key players, in the public and the private sector. Since the end of the last century, many countries have shown a clear

willingness to improve population access to essential medicines by clearly formulating national medicine policies outlined as national targets. Experience shows that such documents are the most valuable if they are developed through a consultation process involving all stakeholders (WHO, 2004). Recognizing that the situation in each state may require specific aims, WHO suggested that the main objectives of the pharmaceutical policy are as follows:

a) Equal access to and availability of essential drugs;

b) Quality, safety, and efficacy of all medicines;

c) Therapeutic and cost-effective use of medicines by medical professionals and end-users.

Although the concept that health and access to pharmaceuticals play a central role in human development has become self-evident across all types of literature, there is limited research focused on the particular state systems that ensure the quality standards for medicines. This is particularly remarkable in terms of the relationship between globalization and the genesis of international norms for pharmaceutical quality. In the area of pharmaceutical regulation, almost all cross-national empirical research has focused on intellectual property rights, leaving aside the question of the government's capacity to regulate the pharmaceutical market and variations in regulatory practices across countries (Pezzola and Sweet, 2016). Although many recent studies have made considerable contributions to our understanding of the global and national pharmaceutical markets, their specific attention to pharmaceutical ownership rights has overlooked the capacity of states to regulate the quality issues of the medicines consumed by their citizens. Evidence shows, however, that although countries have been transforming their norms on intellectual property, they have also been undergoing a deep regulatory restructuring of their pharmaceutical markets in terms of product registration procedures and respective laws. In addition, the system of medicines post-authorization oversight and PV may prove to be the next borderline of international negotiation sources for access to medicines.

The current trends in research on global pharmaceutical regulation and the access to medicine focus on the construction of several indices that improve our understanding of how regulation of medicines is changing in the developing legal environment. Using item response theory based on regulatory quality, a cross-national measure of regulatory quality, and the estimate of variation within and across countries has been investigated (Pezzola and Sweet, 2016).

2.6. Issues evaluating pharmaceutical regulatory policy

State officers and the public deserve to seek knowledge concerning not only how well their regulations work, but also how well their regulatory policy performs in general. The question arises as to whether the legislative requirements that demand analysis or transparency in the development of new regulations make a difference to society. To evaluate the regulatory policy directed at how regulations are developed, evaluations will actually need to follow a framework identical to the one used for evaluating the regulations themselves. The logic behind causal mapping applies to the efforts to evaluate regulatory policy as well as the regulation itself.

Thus, pharmaceutical regulatory policy as any other policy is a type of regulation or way of regulating the regulators. In other words, it is regulation inside the government. The aim of pharmaceutical regulatory policy is to remodel behaviour to improve outcomes such as prices, affordability, and availability. Therefore, the behaviour sought to be changed by the pharmaceutical policy is that of the regulatory institutions or that of the officers working for such institutions. Considering the similarity in the causal logic of both regulation and regulatory policy, anything that can be mentioned regarding evaluating regulation will apply to the evaluation of regulatory policy. Law and regulatory policy are both approaches used in any program evaluation. If better outcomes from pharmaceutical regulations are the ultimate outcome of concern for the policy, the only way to evaluate such a policy would be to consider distinguishing if the laws themselves are better (Coglianese, 2012).

Therefore, to evaluate the regulatory policy concerning medicines in the RF after 2010, we will need to include an evaluation of the MA effectiveness under adopted requirements.

To define whether transparency essentials really do improve the notable outcomes of pharma regulations by making it more difficult for officials to adopt inefficient or ineffective regulations that favour special interests, an inquiry must be built into the substantive quality of rules. Doing so is necessary, as regulatory policy; aims to improve particular regulations incorporated within a full evaluation of regulatory policy will be an evaluation of regulations themselves. Therefore, methods of evaluating regulatory policy are not just analogous to methods of evaluating definite regulation; they actually depend on them.

In summary, the reasonable assumption that regulatory policy often concerns itself at least to some degree with the substantive performance of a particular legislative act, the evaluation of the act itself will be more than just analogous to the evaluation of the policy. It will be integral to ensure the betterment of the policy (Coglianese, 2012).

2.7. National pharmaceutical regulatory policy in the RF

The Russian pharmaceutical market was one of the most dynamic and fastest growing global markets in the beginning of 2009. The sales of pharmaceutical products in the RF in 2007 amounted to approximately 298 billion rubles in final consumption prices, whereas in 2008, the sale amounted to approximately 360 billion rubles. Moreover, the market's growth potential was quite substantial: an annual growth of at least 10%–12% per year in rubles was reported since 2003. As a result, the market volume, considering the financial and economic situation, was expected to reach 400–500 billion rubles by 2011 and 1000–1500 billion rubles by 2020 (final cost for consumers). When fulfilling the state task of achieving the average European level of drug consumption per capita and increasing the population to 142–145 million as planned per the Concept of Long-Term Socio-Economic Development of the RF for the period up to 2020 (Прав. Рос. Федерации, 2008), the size of the pharmaceutical market was expected to reach 1.5 trillion rubles by 2020 (Мин Пром, 2009). Further, the volume of the Russian pharmaceutical market in 2018 reached 1.682 trillion rubles and the sales volume of drugs in packs increased by 1.5% and amounted to 6.4 billion packs (Шуляк *et al.,* 2018).

It is a common assumption that daily activity, vitality, and life expectancy of the country's population has a direct and immediate connection with the health of any nation. These factors are significantly influenced by the circulation of medicines. Of particular importance in circulation, is the quality and accessibility of medicine, which depends on import and domestic manufacturing. The state regulates both processes through the adoption of legal norms covering various aspects: from the procurement of medicinal raw materials to the use of finished dosage forms, and that applies to both medical institutions and individual use. Considering mentioned, the aspects of law enforcement are becoming relevant when considering problems that arise in the current system of procurement of medicines, control of their quality, availability, and free provision of medicines, which ultimately can be harmful to the citizens' lives.

According to the Constitution of the RF (*Конституция Российской Федерации*, 1993) everyone is guaranteed the right to have the protection of health and medical care, which is impossible without the use of medicines. This explains the value and importance of medicines in the consumer market of the RF. To ensure the availability of high-quality, effective, and safe medicines for the population, in 2009, the state represented by the Ministry of Industry and Trade declared strategies of the pharmaceutical industry of the RF for the period until 2020 (Мин Пром, 2009).

One of the aims and objectives of the Order (Мин Пром, 2009) was to improve the system to confirm the quality of medicines, including measures to remove excessive administrative barriers to the registration of domestic medicines and to ensure proper quality control. Another purpose of the order was to harmonize Russian standards for the development and production of medicines with international requirements to increase the competitiveness of the domestic pharmaceutical industry.

3. Materials and methods

The present research is based on a case study approach, which is particularly useful when there is a need to obtain an in-depth appreciation of an issue, event, or phenomenon of interest, in its natural real-life context (Crowe *et al.*, 2011). We employed a mixed methods research in which our team combined elements of qualitative and quantitative research approaches (e.g. use of qualitative and quantitative viewpoints, data collection, analysis, inference techniques) for the broad purposes of deep understanding and corroboration of the issue analysed (Schoonenboom and Johnson, 2017). We tried to explain, explore, and describe events behind the introduction of NPL in an everyday context of occurrence. We also tried to understand and explain causal links and pathways resulting from the new RF regulatory policy initiative. According to literature, we focused on the main stages of research activity to plan and undertake our case study. We assumed the crucial stages: 1) defining the case, 2) selecting the case, 3) collecting and analysing the data, 4) interpreting data, and 5) reporting the findings. To develop a thorough understanding of the present case, we involved t collection of multiple sources of evidence, using a qualitative technique such as critical literature review and quantitative (e.g., collected MA and safety reporting data). The use of multiple sources of data (data triangulation) has been advocated as a way to increase the internal validity of a study (i.e. the extent to which the method is appropriate to answer the research question), assuming that data collected in different ways should lead to similar conclusions, and approaching the same issue from different angles can help develop an interconnected picture of the phenomenon (Crowe *et al.*, 2011).

3.1. Systematic literature review of pharmaceutical legislation of the RF as qualitative research method

As a systemic review is an important research method, we decided to employ this approach as the basis of the present study.

According to Russel (Russel *et al.*, 2009), a systematic review is a protocol-driven comprehensive review and synthesis of data focusing on a topic or related fundamental questions. It is typically performed by experienced methodologists with the input of domain experts.

We followed the recommendation that the first step in conducting a systematic review is to formulate specific vital questions. For situations that address more than a single, simple question, it is often useful to construct an analytic framework (evidence model) depicting the

core issues being addressed to help appreciate their relationships (Russel *et al.*, 2009). The question addressed was how did the regulatory environment in the RF change after the introduction of NPL?

To perform the present critical reviews, we took into account guidelines produced by the Cochrane Collaboration (version According to the background, review questions, search strategy, methods of study selection, quality assessment, data extraction and synthesis, and the timetable (Higgins and Green, 2008) and prepared a study protocol as described below.

As an additional research methodology in the literature review, formal logic analysis which includes synthesis, comparison, analogy, abstraction, generalization, formalization, induction, and deduction was used.

3.1.1. Objectives of the review

An objective of the review was to analyse the regulatory framework governing MA of pharmaceuticals in the RF based on a review of national documentation governing approaches to assess the effectiveness, safety, and good manufacturing practices of drugs. Another objective was to compare Russian regulatory guidelines with those existing in the European Union and the Eurasian Union. As far as quantitative research was used for further statistical analysis to evaluate NPL's legislation performance, we also analysed documentation governing approaches to assess the effectiveness and safety of FS. According to the main stages of research activity (Crowe *et al.*, 2011) a synthesis of the outcomes of the selected findings was presented yearly at professional seminars to enhance the practical implementation of a pharmaceutical MA process. In addition, articles in the scientific press were published regularly. PV safety reporting data, from the European Union and the RF, were collected.

3.1.2. Inclusion criteria

Types of literature data included in the review

The following types of literature were eligible for inclusion:

- legislative acts regulating social relations arising from the MA of pharmaceuticals and PV in the RF
- legislative acts regulating social relations arising from the PV in the European Union

- legislative acts regulating social relations arising from the MA of pharmaceuticals and PV in the Eurasian Economic Union
- Literature data on the practice of applying such norms, as well as scientific and theoretical work on social relations arising from the circulation of medicine
- legislative acts regulating social relations arising from the MA of FS in the consumer market of the RF
- Literature data on the practice of applying such norms, as well as scientific and theoretical work on social relations arising from the circulation of medicines and PV
- systematic reviews related to the above-mentioned data

As seen from the above-mentioned information, a triangulation of data sources was used to reveal to ensure (Hyett, Kenny and Dickson-Swift, 2014) the study is meticulously detailed.

Documents analysed

All the norms of the legislation of the RF and Eurasian Economic Union (EAEU) regulating MA of medicines or FS in the consumer market of the RF, as well as PV, the practice of applying such norms, and scientific and theoretical work on the topic of the present research.

3.1.3. Exclusion criteria

According to the steps of review:

a) documents not related to the norms of the legislation of the RF regulating MA of medicines or FS, or PV in the consumer market of the RF

b) documents not related to the norms of the legislation of the RF regulating MA of medicines and pharmacovigilance in the consumer market of the European or Eurasian Union

3.1.4. Types of outcomes

As outcomes, any evidence of the function of the regulatory framework governing marketing authorization of pharmaceuticals or food supplements in the Russian Federation for

the research were concerned. Any evidence of the function of the regulatory framework governing marketing authorization of pharmaceuticals and pharmacovigilance in the European and Eurasian Union was concerned.

3.1.5. Search strategy

The following electronic databases were searched for relevant documents:

One of the largest legal information structures in Russia Консультант Плюс – http://www.consultant.ru

The legal system "Guarantor" – http://www.park.ru

Eurasian Economic Union – http://www.eaeunion.org

https://grls.rosminzdrav.ru/Default.aspx

https://www.ema.europa.eu

https://www.rosminzdrav.ru/

http://www.remedium.ru

http://www.medlinks.ru

http://docs.pravo.ru/

http://www.rg.ru

http://www.pharmvestnik.ru

http://vademec.ru

http://eurasiancenter.ru

http://www.roszdravnadzor.ru

http://adilet.zan.kz

http://publication.pravo.gov.ru

http://docs.cntd.ru

https://www.gost.ru

http://rospotrebnadzor.ru

http://base.garant.ru

http://fsa.gov.ru

http://cgon.ru

Other more region – or subject – specific databases were also searched.

http://www.ClinicalTrials.gov

The main search items are shown in the table as below.

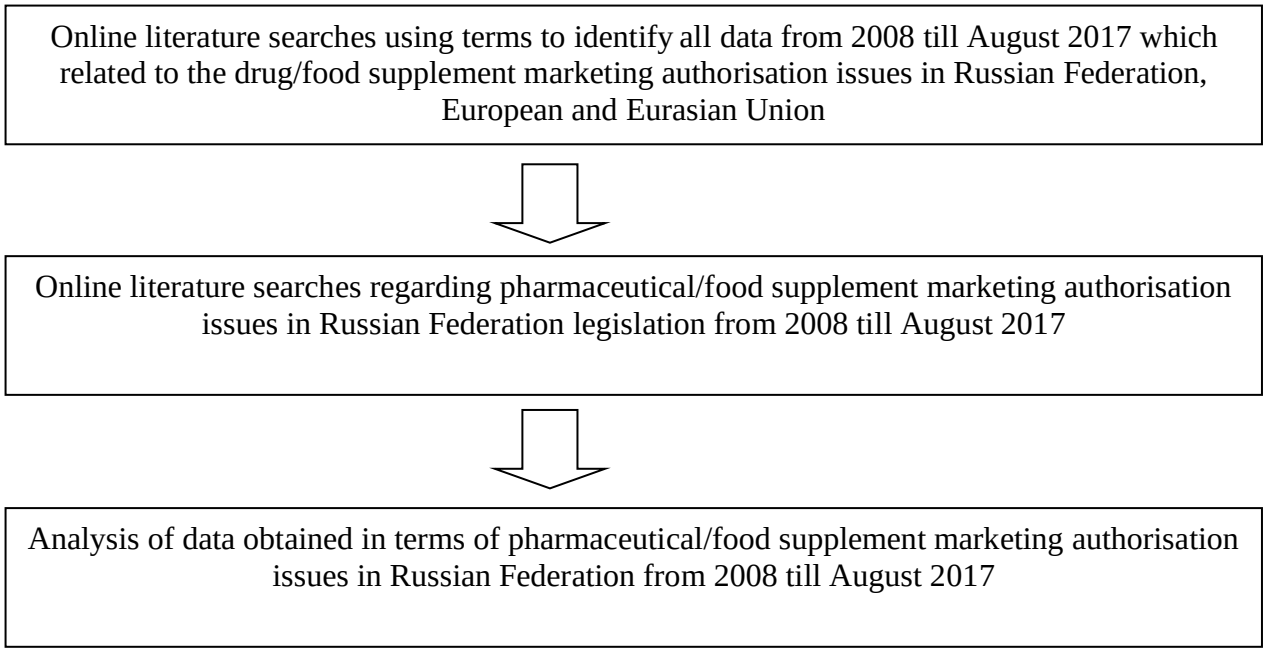
Table 3.1.

Main search terms

Search terms
Регистрация лекарств
Об обращении лекарственных средств
Биологически активные добавки
Евразийский союз
Marketing authoristaion drugs
CTD format requirements
Новый закон Об обращении лекарственных средств

Search limits: Russian, English languages only.

A schematic of the processes of the systemic review



3.1.6. Data extraction

Data were extracted from the papers identified using a structured data extraction form (Table 3.2). Given the limited time and resources available for the review, this was a simple

text-based form in the word processing package MS Word/Excel. The data were entered into the form electronically to facilitate data summarization and the writing of the final report. The sample data extraction form is shown below.

Table 3.2.

Data extraction form

Date	Document name	Short description	General outcomes

3.1.7. Quality assessment

According to the investigator triangulation approach (Archibald, 2016) one reviewer assessed quality, and a second reviewer double-checked a proportion of the assessments. Disagreements were resolved by consensus or by consulting a third reviewer, if necessary.

Review assessment was based on the PRISMA statement (Moher *et al.*, 2009):

- inclusion criteria described (study design, participants, interventions, outcomes),
- details of literature search given (databases, dates, keywords, restrictions),
- study selection described,
- data extraction described,
- study quality assessment described,
- study flow shown,
- study characteristics of individual studies described,
- quality of individual studies given,
- results of individual studies shown.

3.1.8. Analysis

Descriptive analysis

The key purpose of the analysis was to comprehensively evaluate the MA process and PV reporting of medicines in the RF, identifying problems in the legal regulations, and the development and implementation of theoretical and practical provisions for improvement to follow the legal pathways of the authorization and safety reporting process (SR). The author's personal involvement in the MA process was a part of the analysis of direct observation.

A narrative synthesis of the outcomes of the selected papers included the following:

1) type of paper,

2) baseline and final outcomes of interest,

3) outcomes: conclusions of papers,

4) practical recommendations for the performance of tasks related to pharmaceutical MA in the RF.

The descriptive analysis with recommendations was compiled in summaries, referenced with appropriate legislation, and was uploaded online at the dedicated website www.inforeg.eu (Inforeg, 2020). Access to the website is restricted to registered users only.

3.2. Statistical data analysis as quantitative research method

To evaluate the quantitative impact of NPL on the number of registered medicines, issued MAs, and PV activities, we employed a quasi-experimental design. We used longitudinal data from NPL impacted and control groups to have an appropriate counterfactual estimating a causal effect for the MA numbers and PV activities.

3.2.1. Indicator of regulatory performance

By evaluating pharmaceutical legislation, the research presented must answer whether a legislative act can ensure the reduction of a stated problem.

Thus, the performance indicators concerned were the following:

a) Impact of regulation on access to medicines in terms of total and per year quantity of registered medicines during the implementation of the NPL;

b) the number of adverse side effects reported at the same time.

We choose the above mentioned indicators as meaningful indicators of regulatory performance as they can potentially help draw the attention of the professional society concerning the opportunities for improvements across different regulations and the assessment of whether these indicators are involved in the mitigation of health risks.

3.2.2. Data availability

We had available and compiled data in our possession. The data already existed in an available dataset and were considered as the easiest to use. A longitudinal collection of excel sheets issued by the State Medicines register of the RF, counting all authorized medicines, were available for defined years, before and after the introduction of the NPL.

The data regarding the parallel trend assumption were taken from available data from literature.

For the parallel trends assumption, a following data table was used.

Table 3.3.

Parallel trends assumption time for MAs

Year	Numbers of issued Mas per year	Numbers of MAs
Drugs		
2005–2009		
Food supplements		
2005–2009		

As far as the PV system began to function effectively only in 2009, parallel trends were observed from 2009 to 2010, as shown in the table below.

Table 3.4.

Parallel trends assumption time for PV

Year	Number of SAEs /1000 inhabitans/ per year
RF	
2008–2010	
EU	
2008–2010	

As seen from the tables below, two times were chosen for MA DiD analysis for the years 2008 and 2012, respectively.

Table 3.5.

DiD calculations for Mas

Year	Numbers of issued Mas per year	Numbers of MAs
Drugs		
2008 and 2012		
Food supplements		
2008 and 2012		

For the PV activities, a different first year was chosen due to the insignificant reporting activities in the RF in 2008.

Table 3.6.

DiD calculations for PV reports

Year	Number of PV reports / 1000 inhabitans / per year
RF	
2009 and 2012	
EU	
2009 and 2012	

3.2.3. Causal attribution to MA regulation

To answer whether the NPL led to positive improvements concerning access to medicine and SR, we used data sets *before* and *after* the introduction of the NPL. That is, before and after the adoption of regulations. Both data groups were not randomly assigned and could not be viewed as equivalent. Therefore, the confounders were controlled.

3.2.4. Control of confounders

To account for confounders in the regression analysis, we used DiD estimation. A quasi-experimental design using longitudinal data from treatment (NPL impact) and control groups to have an appropriate counterfactual to estimate a causal effect for the MA numbers and PV activities was used. Quantitative research was used for further statistical analysis to evaluate NPL's legislation performance; and the study analysed documentation governing approaches to assess the effectiveness and safety of FS. Therefore, the following control group was selected: for registered medicinal products, FS registered in the RF were chosen. This control group was found to be appropriate because the MA schemes for both product groups were similar until the adoption of the NPL. Thus, the quality and safety of both medicines and FS were tested during registration. All administrative activities were performed within one ministry and a single institution subordinate to it. Many national market research publications also mention the FS market as a segment of the overall pharmaceutical market (Лин, 2014). In contrast, after the NPL, the authorization process of FS did not change, but the confounders important for DiD analysis, which influenced the dependent variable (number

of registered medicines) and the independent variable (number of FS) were similar and nationally specific.

The performance of the European Medicines Agency was chosen as a control group for the PV assessment. The choice was justified because the PV activities described by the NPL were similar to the European Union (EU), alongside the fact that comparison within the RF was not possible. There were no significant legislative changes to the EU PV reporting system during the study period. Thus, the confounders affecting PV activities in the RF and EU would be similar. The detailed description and reasons for the suitability of the above-mentioned approach are discussed in the Results section.

The regression equity for both number of authorized items and SRs was as follows:

$$\mathbf{Y = \beta\_0 + \beta\_1 \cdot T + \beta\_2 \cdot FI + \beta\_3 \cdot (T \cdot WFI) + e}$$

Where:

Y is the number of items included in the drug or FS registers as well as SRs in each time period, *T* is a time dummy, FI is a FS dummy, and $T \cdot FI$ is the interaction of the time dummy and the FS dummy.

The "e" is a random, unobserved "error" term, which contains all determinants of *Y*, which the model omits. The error term is, on average, zero: $e = 0$

The table below displays the items included in each register and the time period.

Table 3.7.

Table for DiD calculations for issued marketing authorisations

	Drugs	**Food supplements (Control)**
Year 1 (2008)	a	b
Year 2 (2012)	c	d

Table 3.8.

Table for DiD calculations for PV activities

	Safety reports in Russia	**Safety reports in EU(Control)**
Year 1 (2009)	a	b
Year 2 (2012)	c	d

The next table explains what each coefficient in the regression represents.

Table 3.9.

Table for DiD calculation explanation

Coefficient	Calculation
β_0	a
β_1	c – a
β_2	b – a
β_3	(d – b) – (c – a)

As seen above, β_0 is the baseline average, β_1 represents the time trend in the control group (FS), β_2 represents the differences between the two legislations in year 1, and β_3 represents the difference in the changes over time. Assuming that both legislations have the same environmental trends over time, we have now controlled for a possible national time trend. We can now identify the true impact of the NPL on the number of medicines registered.

For DiD to be a valid statistical method, we considered several assumptions. In order to estimate any causal effect, three following concerns were followed: exchangeability, positivity, and Stable Unit Treatment Value Assumption (SUTVA) or the potential outcome observation (Schwartz, Gatto and Campbell, 2012) on one FS unit should be unaffected by the particular assignment of treatment (NPL) to the pharmaceutical legislation.

We did not use ANOVA as it was used to compare three or more group means where the participants were the same in each group (Laerd Statistics, 2020). In our research, two groups of means were analysed.

4. Results

4.1. Marketing authorization pathway till 2010

Further, we shall describe drug registration pathways in power in the Russian Federation until the introduction of NPL. There will be an insight given into the practical issues caused by the implementation of the new marketing authorization law from 2008 until 2012.

The old pharmaceutical law issued in 1998 (Федеральный закон, 1998) was amended eight times within ten years. To 2015, NPL had already been revised 19 times. The reasons for the frequent amendments, as well as consequences, are provided.

The main legislative acts dealing with the international issues around the pharmaceutical authorization process since 2006 was Civil Code of the Russian Federation Part Four (Государственная Дума, 2006). At that time, Russia was not a member of the World Trade Organisation (WTO), did not provide data exclusivity and not distinguish between pharmaceutical originators and generics. There even was no term generic in the legislation. International and Russian Patents were only valid if granted by RosPatent (Russian Patent Agency). Generics were approved only after the expiration of the applicable original medicinal product patent. Contrary to Trade-Related Aspects of Intellectual Property Rights Article 39.3 (WTO, 1995) the legislation allowed for unfair commercial use of clinical trial data.

The main acts regulating the procedure of MA were The Federal Law on Medicines of 1998 (Федеральный закон, 1998), The Federal Law on Technical regulation of 2002 (Государственная Дума, 2002a) describing standards in technical processes of evaluation of the drugs and processes.

The Order of Ministry of Health (MOH) No. 736 of 2006 (Министерство здравоохранения и социального развития, 2006) outlined administrative procedures of MA process. Consecutive Orders and Letters made the changes into the proceedings and instructions of the MOH.

It was its own unique regulatory system, which did not completely comply with U.S. or European practices however used to follow its general principles.

The state registration included the following stages:

1) assessment,

2) pre-clinical,

3) clinical assessment,

4) approval of the normative documentation (ND) for pharmaceuticals.

The functional scheme of State Authorities involved in the MA process is shown in the Figure below.

Figure 4.1. State Authorities involved in the MA process

The acting authority which performed dossier evaluation was the Scientific Centre for Expertise of Medical Products (FGU). There were 35 employees at the FGU in 2009 who succeed evaluate 2000 MAs per year. However, that was not only the success of FGU but the following fact. According to WTO requirements (WTO, 1995), Russia was decentralizing pharmaceutical evaluation prior to registration. The monopoly of FGU to drug evaluation was limited. There are so called non-commercial organizations (NCO) which had legal rights to do pre-registration evaluation of drugs. There were 18 NCOs that signed agreements with FGU regarding pre-registration evaluation of drugs in 2009. Thus, the dossier evaluation was outsourced to different subcontractors, which substantially decreased evaluation time and quantity. A simplified scheme of MA process outflow is shown in Figure 4.2.

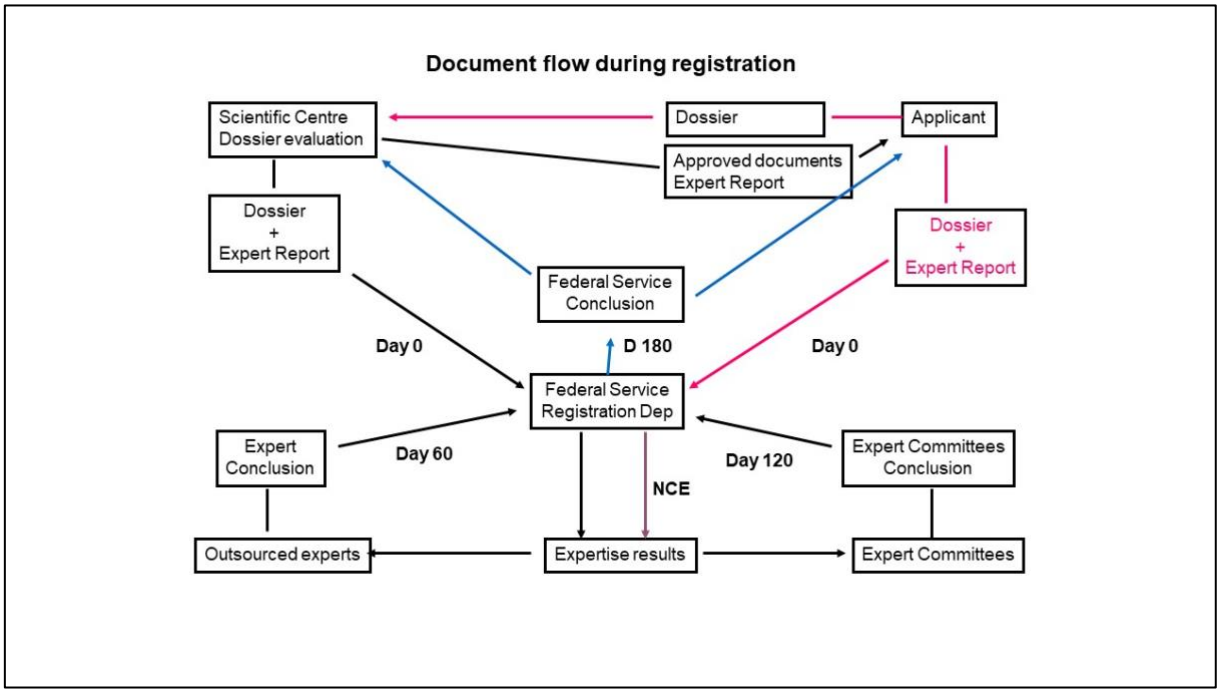


Figure 4.2. A simplified scheme of MA process

4.1.1. The rationale for NPL

As it was stated in the press, the Russian pharmaceutical market continue to attract foreign investors in the ensuing years because of steady growth rates, which were significantly higher than those in the Western markets, and because of the existence of the State program for the development of the country's pharmaceutical industry until 2020, known as Pharma 2020 (Прав. Рос. Федерации, 2008). Certain analysts estimated that by 2020, the Russian pharmaceutical market achieve a value of US $ 60 billion, with an annual growth rate of at least 15%, which was attractive to foreign investors (The Pharma Letter, 2013). The latest prognosis provided the same figures. Thus, according to estimates by IMS Health, the volume of the Russian pharmaceutical market in 2015 was expected to increase by 12% to 18% compared to 2014 and achieve 1.286 trillion roubles (US $ 16.3 billion; exchange rate of January 25, 2016) (Markova, 2015). Nevertheless, the frequent changes in regulatory legislation made the process of marketing authorization in Russia much more challenging than in Europe. The most defiant time for regulatory affairs specialists was 2010, when a new law, Federal Law No. 61-FZ "On Circulation of Medicines" dated April 12, 2010, was announced.

In the beginning of 2010, the Minister of Health and Social Development, Ms T. Golikova, convinced the government of the merits of the draft law, "On Circulation of

Medicines", and the deputies of the State Duma Committee on Health recommended the adoption of the document in the first reading. However, during Golikova's meetings with the people's elected representatives, the project was criticized more than praised. The Minister was convinced that the new law would create conditions for fair competition in the domestic pharmaceutical market for both Russian and foreign manufacturers. She stated that the main point of the project was the conceptual alignment of market conditions for domestic and foreign manufacturers. In that situation, since the old law (OL) was issued in 1998 to regulate the drug circulation, the domestic producers had discriminated against foreign producers. The requirements of the NPL will balance the rights of domestic producers with those of foreign producers (Шкель, 2010); ((Lozda, 2016). The Minister also stressed that the current procedure for registration of medicines was not transparent. The NPL fundamentally changes this procedure and establishes a single authority and responsibility for the registration procedure; it also states that the duration during such registration must not provide a chance to delay this process. The NPL establishes a single State fee for the State registration of medicines. Any other fee for any procedure is eliminated and prohibited by law. Any requisitions from the manufacturers will not be possible.

Among other favourable arguments, the Minister noted that the law clearly designates the period of time allowed for the registration of the drug. The maximum term is 210 days, with a maximum of 60 days for generics. All of the information on the registration procedure of medicines will be published on the website site of the authorized federal body (Медвестник, 2009); (Lozda, 2016).

4.1.2. The first months under new legislation

Compared with the OL of 1998, the new law contained several improvements in terms of definitions. For example, in the OL, original medicines were drugs put into circulation with their own registered names and reproduced medicines put into circulation after the expiration of exclusive patent rights to the original medicines (Lozda, 2016).

According to the new definition, an original medicine is a drug that contains a first obtained pharmaceutical substance or a new combination of pharmaceutical substances whose effectiveness and safety is confirmed by the results of preclinical studies and clinical trials of drugs. The reproduced medicine is the drug that contains the same pharmaceutical substance or a combination of the same pharmaceutical substances in the same dosage form as the original drug, which was put into circulation after the original drug entered circulation.

Despite a superficial description of the key terms in the 1998 legislation, the system of marketing authorizations in the Russian Federation worked satisfactory till the beginning of 2010. The institution, FGU, was responsible for the dossier expertise and to compensate for deficiencies in the legislation for many years by issuing letters and recommendations in the form of memos for applicants. These documents contained detailed descriptions of procedures and dossier requirements. In the best case, applicants received marketing authorization for generic products within nine months from the initial application.

The new legislation changes anticipated the overtaking of the FGU functions by the Ministry of Health and Social Development of Russian Federation (MHSD). All recommendations and memos also lost power at that time (Lozda, 2016).

The most significant outcome of the NPL was the requirement for local clinical trials. Due to legislation, the State registration of drugs was based on expertise results and the ethical review of the possibility of clinical studies of the drug. The State registration consisted of two stages. The first stage was the examination of documents to obtain permission to conduct a clinical study of the drug, except as follows: a) drugs that have been permitted for medical use in the Russian Federation for more than twenty years and for which the study of bioequivalence is impossible; and b) drugs in respect of which international multicentre clinical trials were conducted and some of these studies were held in the territory of the Russian Federation (Lozda, 2016). Thus, all medicines, including generics, were obliged to undergo clinical trials in Russia. The second stage of registration assumed examination and employment of the proposed methods of quality control of the drug as well as examination of the risk/benefit ratio of the drug usage based on the outcomes of the clinical trial.

Interestingly, and in reference to clause 5, article 3 of the NPL in the RF according to mutual international treaties and (or) based on the principle of reciprocity, the results of clinical trials of medicines that were conducted outside the territory of the Russian Federation are recognized. This sentence caused much expectation in the pharma industry; hover, there was no legal background regarding clinical trials because they could not be the subject of an international treaty because they were not the outcome of activities of government agencies. At the beginning of 2010, there were no international treaties in force related to the mutual recognition of clinical trials (Lozda, 2016).

The former marketing authorization scheme was generally in accordance with the international approach; however, after 2010, a unique authorization system was created.

The NPL was announced on 12 of April 2010 and would enter into force on 1st of September 2010. In addition to basic peculiarities of the NPL, several minor issues caused serious concerns among the pharma industry. Therefore, changes in the outer labelling were

requested, and the registration number of medicines was required to be noted. Negligible variations caused inextricable tasks because an implementation due date for the requirements of 1st of September 2010 did not allow sufficient time to submit a variation, receive approval and produce a new label. In August 2010, serious concerns regarding the situation were discussed in the mass media. It was noted that pharmacists would not have time to change the packaging time and, according to experts, this process could take approximately 9–12 months. Thus, medicines in packaging that was produced in Russia or imported after the law entered into force will become impossible to sell because of noncompliance; the Roszdravnadzor could revoke the registration certificate (Медлинк, 2010); (Lozda, 2016).

Consequently, the NPL was amended on 27 of July 2010 prior to entering into force. This amendment contained certain minor clarifications in several articles.

One month after the NPL was enforced, another amendment followed in which issues related to clinical trials and medicine pricing were discussed. The most significant changes were related to the registration dossiers submitted before the date of entry into force of the NPL. It was set that the State registration and examination of dossier for such drugs is conducted on the basis of documents and data initially submitted without requiring the payment of new State fee, as specified in the NPL and the related legislation. The transitional period of submission was established on 1st of March 2011.

This practice differed from the one known within the EU and requires an explanation.

From the 1st of September 2010, the authority engaged in the registration of medicines became MHSD. Formerly, these activities were performed by the Roszdravnadzor. As noted above, the examination of dossiers was performed by FGU. Without FGU's conclusions, MHSD did not accept documents that were submitted for final approval prior to the NPL. To receive such a conclusion and submit it to the MHSD, a transitional period was set. This process related to the new marketing authorization submissions, renewals and variations.

Another change was related to the implementation of the new labelling requirements. The transitional period was also defined as 1st of March 2011.

Two more NPL amendments followed through the end of 2011; both were enacted on 29th of November 2010. The key changes were related to the insurance of clinical trials, the definitions of cases to pay State fees and the transitional period for dossier submissions according to the former legislation (Lozda, 2016).

4.1.3. Regulatory outcomes in 2011–2012

The following year, 2011, was really challenging for regulatory personnel as well as State officers in terms of implementing the NPL.

There were approximately 9000 dossiers under evaluation in the FGU before 1st of March 2011. In particular, 1500 dossiers were supplied before 1st of September 2010. The FGU did not have time to process all of the files; it addressed 300 sets of documents at the same time, while receiving another 50 new ones weekly. The FGU failed to confirm these figures. In response to a written request by the newspaper, "Vedomosti", the authority advised seeking comments from the MHSD. The Ministry spokesman confirmed that there were nine thousand dossiers under evaluation in the FGU; however, it did not answer the question regarding whether the centre had time to process all of the files by March 1st. It was noted that those companies failed to obtain the opinion of FGU and submit the documents to the MHSD by March 1st would be obliged to pay State duties again (Lozda, 2016).

Double payment was not the sole reason to hasten the submission of the conclusion. A key argument was the avoidance of local clinical trials. In February, the situation became so dramatic that FGU dispensed documents every day from 9 o'clock until the last customer was serviced. One thousand dossiers were prepared for pick up. Regulatory personnel formed queues in front of FGU as well as MHSD (Lozda, 2016).

As a witness to these events, I can note a high level of self-organization among the local regulatory specialists. People were arriving many hours before the MHSD's opening hours, making participant lists of queues to prevent chaos during submission. The event also had no analogies, at least not in the EU regulatory practice.

Finally, the pharma industry participated in parts; the lucky ones achieved submission to MHSD according to the old legislation and the unfortunate one endured double payment and clinical trials (Lozda, 2016).

The NPL legislation requirements around clinical trials during State registration of medicines were also at an impasse. Therefore, the Russian Association of Clinical Trials Organizations stated that the Law was adopted under the slogan "transparent procedures", "standardization", "strictly defined deadlines of State functions" and "increase the availability of drugs for the population". The organization summarized total achievements during the first year of NPL implementation and concluded that the stated goals were not achieved. The law had created serious obstacles not only for development but also for the normal functioning of the clinical trials market. Because of the problems of the transition period in the first months of the NPL, permits were rarely issued. Consequently, in 2010, Russia received less than 100

international studies, which is approximately 25% of the annual market. The deteriorating situation was felt by both the companies and patients who participated in the clinical studies. The similar, if not more complicated, situation occurred within the system of drug registration (Фармацевтический вестник, 2011); (Lozda, 2016).

4.1.4. Legislation amendments in 2012–2014

From 2012–2013, the NPL was amended three times. These amendments did not change or facilitate the registration procedure. Moreover, in May 2012, after the inauguration of the new/old President of the Russian Federation, a new government was formed. Changes were made in the health care system field. The MHSD was transformed into two separate ministries: the Ministry of Health and Ministry of Labour. The new Minister of Health was appointed. Shortly after the appointment, dramatic personnel changes throughout the ministry followed, including in the relevant department of State regulation of the drug market.

From the very beginning, representatives of the new ministry expressed the need for a change in the NPL, which induced the correction of errors. The representatives committed to readily address this issue and accorded priority to new amendments.

Simultaneously, the pharmaceutical community began active discussion on the implications of the necessary changes in favour of the Russian pharmaceutical market. The amendments' project did not appear until the end of the year, which caused widespread disillusion. Contrary to expectations, the amendments proposed by the MOH did not incorporate any of the offerings from the industry associations and experts from the pharmaceutical market; therefore, it remained a deficient registration system that contained artificially assigned local clinical studies. The sole exception was orphan drugs. In addition, other shortcomings in the current edition of the NPL remained unchanged.

From the practical perspective, the former experience repeated. Thus, pending documents supplied to the MHSD were required to be resubmitted to the MOH, and there were many applicants that were obliged to pay submission fees twice. Regarding the NPL amendments projects that were public available, the society was requested to discuss them and express their views. Despite increased activity from the pharma industry, very few of the countless proposals were considered by the regulatory bodies.

The latest project of amendments in particular, contained significant changes such as the introduction of the concept of "biological drug", "Orphan drug" and others, as well as requirements for the registration procedure. Not only new terms were introduced but also clarification of the existing was anticipated (Шевченко, 2013); (Lozda, 2016).

The situation regarding marketing authorization system in RF was characterized as follows. At the end of 2013, the MOH introduced the sixth edition of amendments to the NPL to the pharmaceutical industry; nevertheless, the amendment implementation process was prolonged. It was believed that the amendments to the NPL would not be accepted for another year and would take effect no earlier than January 1, 2015 (Lozda, 2016).

The most controversial issue that existed in the NPL was the pharmaceutical evaluation process. The process was divided into two stages: a) the first stage was the examination of documents to obtain permission to conduct a clinical study of a drug, and b) the second stage was the examination of the proposed methods of quality control of the pharmaceutical as well as the examination of the risk/benefit ratio of the drug use based on the outcomes of the clinical trial.

This statement means that, contrary to the declared purpose of the NPL, which was to set the priority of the State to regulate the safety, quality and efficacy of medicines, a clinical evaluation of unknown medicines occurred first. The declared priority of safety and quality assurance was performed after an investigation that used people (Lozda, 2016).

4.1.5. Marketing authorization pathway after 2012

Russia become a member of the WTO. The legislation did not allow for unfair commercial use of clinical trial data.

According to NPL the original medicine was a drug, containing first obtained pharmaceutical substance or a new combination of pharmaceutical substances whose effectiveness and safety was confirmed by the results of preclinical studies and clinical trials of drugs. Term “generic” was still not used in the NPL

Instead, reproduced medicine was the drug containing the same pharmaceutical substance, or a combination of the same pharmaceutical substances in the same dosage form as the original drug, and put into circulation after entering the circulation by the original drug.

MA of drugs was based on expertise results and the ethical review of the possibility of clinical studies of the drug. The MA stages were as follows.

The first stage was an examination of documents for obtaining permission to conduct a clinical study of the drug.

The second stage – examination of the proposed methods of quality control of the drug and the quality of the samples controlled by employing methods described in ND or the examination of the quality of the drug and examination of the risk/benefit ratio of the drug use based on the outcomes of the clinical trial.

The MA procedure stages assumed that clinical trials of the drugs are started before their quality assurance.

The functional scheme of State Authorities involved in the MA process is shown in the Figure below.

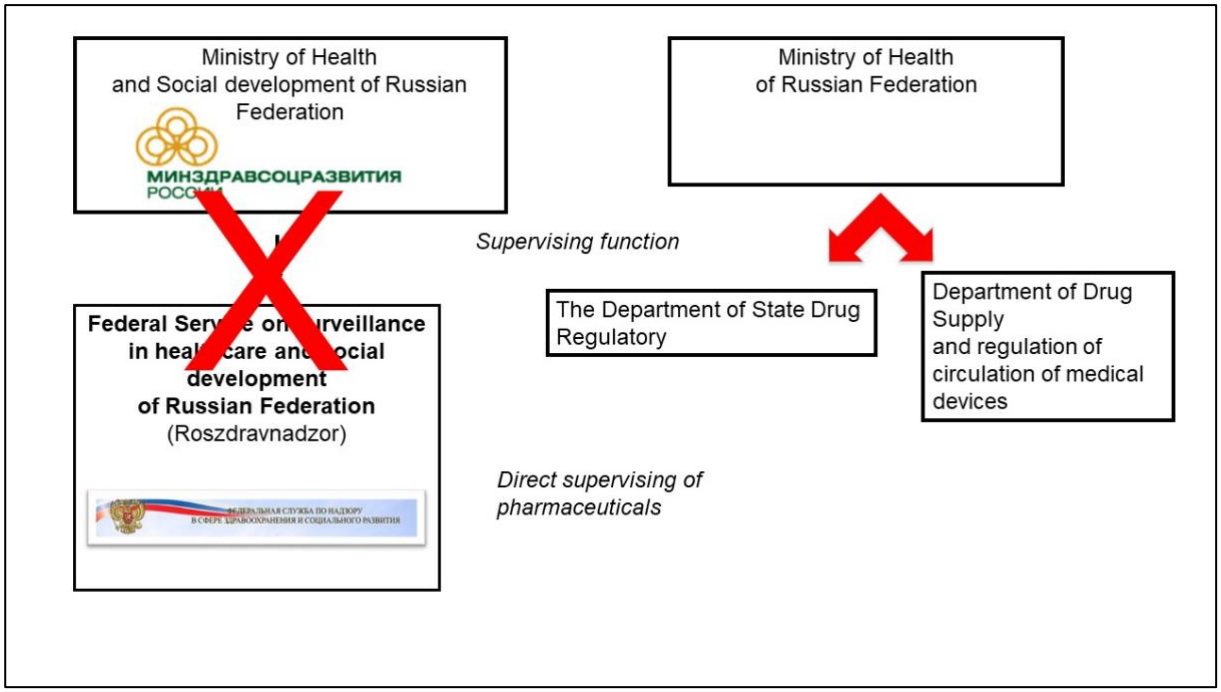


Figure 4.3. State Authorities involved in the MA process

As seen from the figure above, significant changes in the administrative structures were introduced. Ministry of Health and Social Development of the Russian Federation was reorganized. Instead, two ministries establish and the responsible for pharmaceuticals become the Ministry of Health. The dossier evaluation by FGU terminated and subcontracted NCOs excluded from the process at all.

The registration timelines and document flow according to stages are shown in Figures 4.4. and 4.5. below.

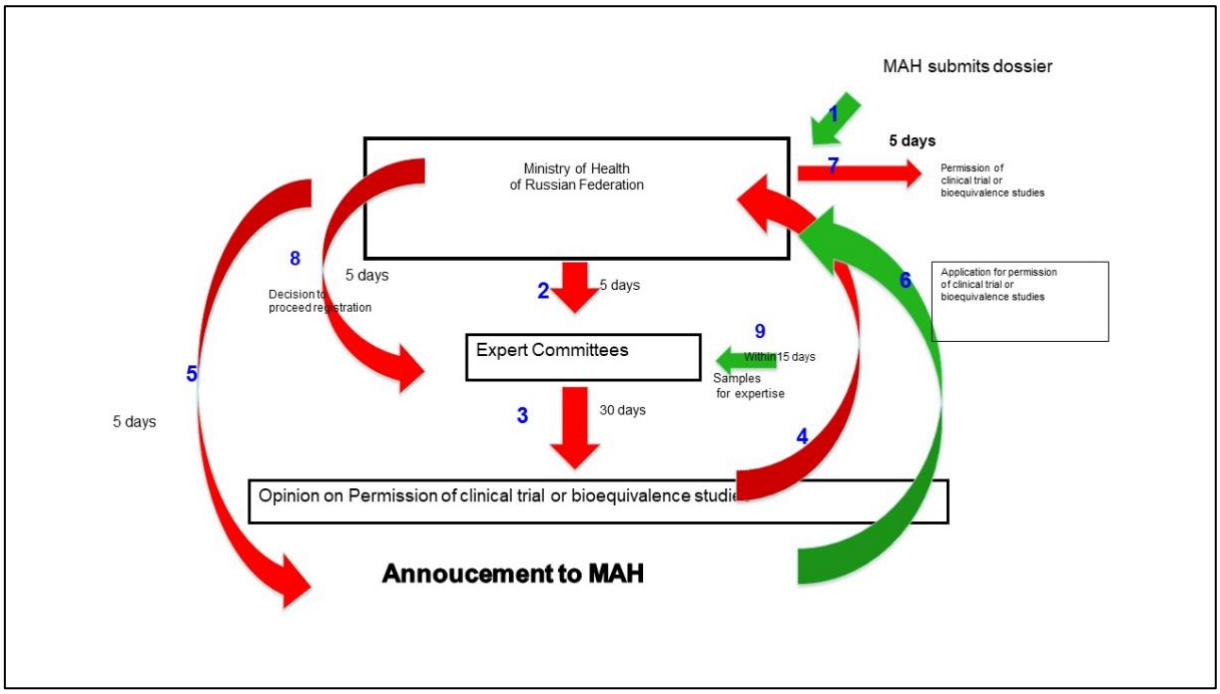


Figure 4.4. MA flow chart for the stage 1

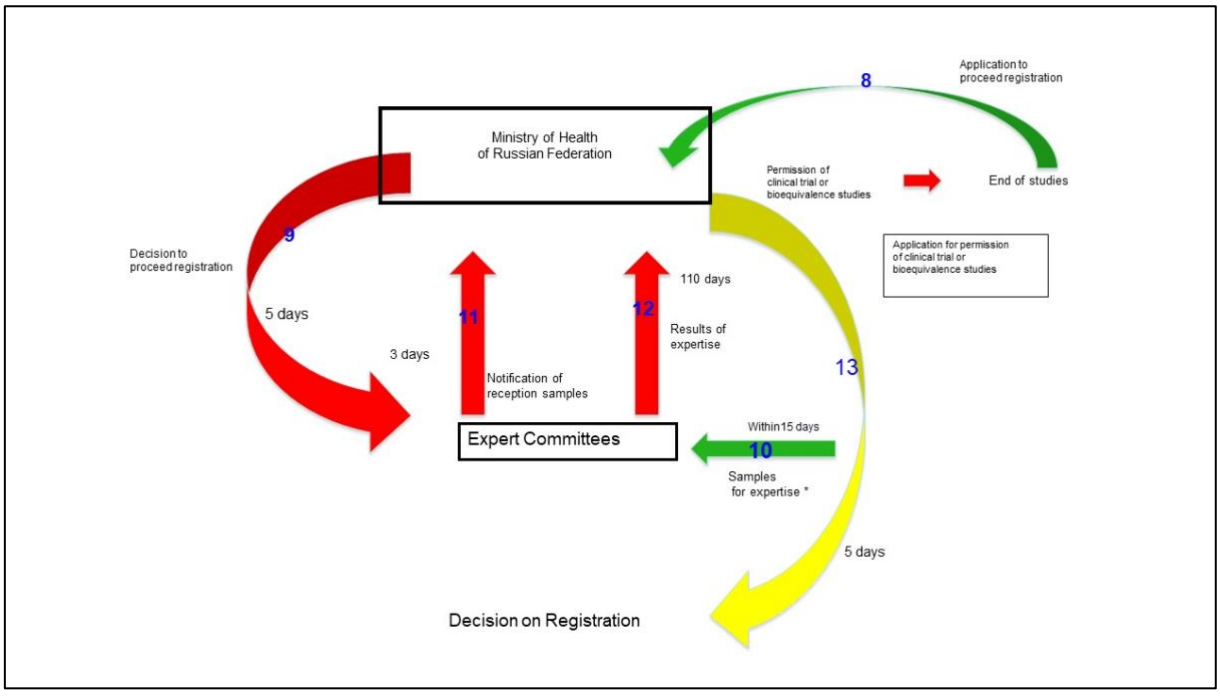


Figure 4.5. MA flow chart for the stage 2

Now the dossier submission was made online at http://grls.rosminzdrav.ru. Manufactures or their representatives must register. The online registration of producers of drugs allowed to apply for state registration of medicines; and tracked the progress of the MA process. To provide access following the submitted e-application, however, the personal

presence still was necessary. The MAH representative must present the original application to the General Division of the Ministry of Health.

There were two types of MA procedures available: standard – for original drugs and accelerated for reproduced drugs excl. immunobiological, insulins, and any newly registered medicine in Russia. Thus, if the drug was concerned as generic in the EU but had no analogues authorized in Russia, it had to pass standard procedure.

The accelerated procedure assumed the submission of a published clinical trial (CT) data and bioequivalence or therapeutical equivalence studies data.

Contrary to the European system, Russian was producer oriented, meaning that term Marketing Authorization Holder had formal meaning. The legal responsibility lied on the manufacturer.

In case when MAH was not producer, a close relationship between them had to be provided.

4.1.6. Descriptive analysis of the unification of the RF procedures within the EAEU

According to the Treaty on the Eurasian Economic Union (ЕАЭС, 2015), a common pharmaceutical market was supposed to become operational on January 1, 2016. Nevertheless, the responsible parties did not meet the deadline. Although a majority of the draft guidelines regulating this process were already known in 2014 and 2015, the anticipated process itself caused anxiety among representatives of the foreign pharma industry, who tried to prepare for coming challenges. Among other possible issues, the ambiguity of transitional periods and a lack of approved legislation were noted. Even until the end of 2016 the market was still not functional. Furthermore, key documents relevant to the market still required approval by the Eurasian Economic Commission, and some of them even required discussion by representatives of the Member States.

4.1.7. The rationale behind unification within the EAEU

The Eurasian Economic Union is an international organization for regional economic integration, and the Member States (MS) are the Republic of Armenia, the Republic of Belarus, the Republic of Kazakhstan, the Kyrgyz Republic, and the Russian Federation. As stated by the Eurasian Economic Commission (EUEC), the pharmaceutical market comprising Belarus, Kazakhstan and the Russian Federation was one of the most dynamic and fastest-growing global markets, achieving a cumulative increase in 2012 and 2013 of 7% and

6%, respectively, and reaching $ 24.1 billion. MS had a relatively small pharmaceutical industry, and the share of the GDP of each country was not more than 0.5%. However, it should be noted that the amount of local production, as well as the total consumption of pharmaceuticals, had been rising in recent years (ЕЭК, 2016a); (Lozda, 2017b).

The general intent in creating the EAEU was to comprehensively upgrade, increasing the competitiveness of and cooperation between the national economies. Another task was to promote stable development to raise the living standards of the nations of the MS by providing free movement of goods such as medicines, services, capital, and labour. The Treaty on the Eurasian Economic Union (TU) and international agreements within the Union will determine single policy in the sectors and harmonize these undertakings (ЕАЭС, 2017); (Lozda, 2017b).

The EAEU carried out its activities within the jurisdiction granted by the MS under the TU. The TU was adopted on May 29, 2014 but took effect on January 1, 2015. Such delay between the adoption and effectiveness dates was required by the fact that the treaty became legally valid from the time of receipt of the last written notification of MS fulfilment of the internal procedures necessary for its entry.

The TU is a highly detailed document of 855 pages and describes the scope of EAEU jurisdiction, as well as policy coordinated or agreed upon among MS and international treaties within the EAEU (Lozda, 2017b).

The TU includes Section VII, Regulation on the circulation of medicines and medical products, where it is stated that MS shall establish a common market for drugs within the EAEU in compliance with the relevant standards of good pharmacy practice based on relevant principles. Furthermore, Article 100 contains a statement that the common market of medicines within the EAEU should function starting from January 1, 2016. It would operate in accordance with an international treaty outlining the common principles and rules for the circulation of medicines (ЕАЭС, 2014), to be signed by the MS not later than January 1, 2015. However, despite the optimistic timeframes stated in the TU, the ratification of common principles and rules at the national level of some MS has extended into 2017 (Lozda, 2017b).

4.1.8. The EAEU regulatory bodies and functions

As defined by the TU, the following collective institutions have been established by representatives of MS: the Supreme Eurasian Economic Council (SC), Eurasian Intergovernmental Council (EUIC), EUEC, and the Court of the Eurasian Economic Union

(CEU). The SC is the supreme body of the EAEU, with the power to make decisions and issue orders. It defines the strategy, direction and prospects of the integration development, makes decisions aimed at implementing the objectives of the EAEU, and determines the procedure for admission of new members to the Union as well as termination of membership in the Union.

Within its scope of powers, the EUEC adopts decisions with regulatory and binding effect for the MS, which form part of the EAEU law and are directly applicable to the territories of the Member States. The EUEC consists of the Council and the Board. There is a Working Group (WG) established by the Board that focuses on common approaches to regulation for pharmaceutical circulation within the EAEU. The WG develops all legislative acts related to pharmaceuticals within the EAEU and proposes them for approval by the Board and additional Commissions.

Decisions, orders, and recommendations issued by the EUEC must be adopted by the Council and the Board. The legislative acts generated are effective no earlier than 30 calendar days after their official publication, or 10 days in some circumstances (Lozda, 2017b). The EUEC prepares the regulatory pathway for pharmaceutical circulation and ensures the uniformity of mandatory requirements for the efficiency and safety of distribution of medicines throughout the territory.

In addition to the above-mentioned regulatory bodies within the EAEU, the governments and presidents of each MS also make significant legal impact. The most notable example related to the role of government establishing a universal pharmaceutical market is the ratification of international agreements.

The first international Agreement to be ratified by the governments of Belarus, Kazakhstan and Russia was the TU. The second was the Agreement on common principles and rules of circulation of medicines within the framework of the Eurasian Economic Union (MCA), adopted on December 23, 2014 (ЕАЭС, 2014); (Lozda, 2017b). The MCA states that this Agreement will enter into force from the date of receipt by the depositary of the last written notification of fulfilment by MS of the internal procedures necessary for its entry into force, but not earlier than January 1, 2016. In other words, to be effective, the MCA required ratification by governments. Thus, interference between national and EAEU legislation led to the delay of MCA implementation until February 2016 (Lozda, 2017b).

4.1.9. Legislative provision in force within the EAEU

As mentioned above, the MCA required national ratification by MS. Table 4.1. below shows the appropriate dates of implementation (Президент Республики Казахстан, 2014); (Прав. Рос. Федерации, 2015); (Президент Республики Беларусь, 2015).

Table 4.1.

National ratification of MCA

Country	National legislation act	Date of ratification
Belarus	Law No. 297-Z On ratification of the Agreement on common principles and rules of circulation of medicines in the framework of the Eurasian Economic Union	July 15, 2015
Kazakhstan	Law of the Republic of Kazakhstan No. 355-V ЗРК On ratification of the Agreement on common principles and rules of circulation of medicines in the framework of the Eurasian Economic Union	October 12, 2015
Russia	Resolution Government of the Russian Federation No. 1325 On submission for ratification of the Agreement on common principles and rules of circulation of medicines in the framework of the Eurasian Economic Union	February 12, 2016

One can see from Table 4.1. that the first country to ratify the MCA was Belarus, and the last was Russia. The national ratification was the fundamental reason for market launch delay and as a consequence prolongation of approval of common EAEU legislative acts occurred. Another fact that continues to cause delay was that Armenia and Kyrgyzstan joined the EAEU later, and all international agreements that had already been ratified on a national level now required a new version. Thus, the MCA must have been ratified once again by MS governments, taking into account both newcomers.

Table below shows the national ratification status of Armenia and Kyrgyzstan's accession to the MCA (Президент Республики Беларусь, 2015); (Президент Республики Казахстан, 2016); (Государственная Дума, 2016).

Table 4.2.

National ratification status of Armenia and Kyrgyzstan's accession to the MCA

Country	National legislation act	Date of ratification
Belarus	Law No. 300-З About ratification of Agreement regarding accession of Kyrgyz Republic to the Treaty on the Eurasian Economic Union of May 29, 2014 and protocols of May 8, 2015	July 15, 2015
Kazakhstan	Law No. 8-VI ЗРК On ratification of the Protocol on the Accession of the Republic of Armenia to the Agreement on common principles and rules of circulation of medicines in the framework of the Eurasian Economic Union of December 23, 2014	July 12, 2016
Russia	Federal Law No. 5-ФЗ On ratification of the Treaty on the accession of the Kyrgyz Republic to the Treaty on the Eurasian Economic Union of May 29, 2014, the Protocol amending the Treaty on the Eurasian Economic Union of May 29, 2014 and certain international treaties included in the Laws of Eurasian Economic Union, the accession of the Kyrgyz Republic to the Treaty on the Eurasian economic Union of May 29, 2014, as well as the Protocol on the conditions and the transitional provisions for the Kyrgyz Republic to the Treaty on the Eurasian economic Union of May 29, 2014, certain international treaties included in the Laws of Eurasian economic Union and the acts of bodies of the Eurasian economic Union in connection with the accession of the Kyrgyz Republic to the Treaty on the Eurasian economic Union on May 29, 2014	July 13, 2015

Kyrgyzstan ratified the TU and MCA together with other relevant documents as a package on accession. Armenia separated the MCA from other documents and required standalone ratification by MS. The country itself ratified the MCA on October 20, 2016. Finally, the present status of the MCA accession was described in the meeting of the pharmaceutical and medical device regulatory working group of the EAEU held in Moscow at the end of 2016. It was noted there that the pharmaceutical community, the authorized bodies of MS and business representatives are awaiting Kyrgyzstan's ratification of Armenia's accession protocols to the MCA. The entry into force of the MCA depends on the Kyrgyz decision (Lozda, 2017).

Certain provisions of the MCA were the second reason for implementation difficulties. The MCA sets out common principles and rules for the circulation of medicines within the EAEU based on other international treaties and legislative acts issued by the EUEC, designing them based on international norms and the legislation of the MS.

Clause 2 of Article 4 of the MCA stipulates that MS shall conduct coordinated policy in the sphere of pharmaceutical circulation by the following means: The adoption of measures necessary for the harmonization and unification of legislation of MS; the adoption of common rules and requirements regulating the pharmaceutical market; ensuring the uniformity of mandatory safety, efficacy, and quality of medicinal products in the territories of MS; a standard approach to the creation of quality assurance systems of medicines within MS; and the harmonization of legislation in the field of pharmaceutical control. The above-mentioned means assumed the preparation of appropriate decisions by the EUEC, which were available as drafts in 2015. However, some of them were not adopted and approved by the Board of EUEC until the end of 2015 (Lozda, 2017).

There were key legislative acts prepared by the EUEC (ЕЭК, 2015a); (ЕЭК, 2015d); (ЕЭК, 2015c); (ЕЭК, 2015b); (ЕЭК, 2018); (ЕЭК, 2016b); (ЕЭК, 2016i); (ЕЭК, 2016c); (ЕЭК, 2016d); (ЕЭК, 2016e); (ЕЭК, 2016f); (ЕЭК, 2016g).

Taking into account all the above-mentioned elements, the MCA needed to be fully ratified by MS with regards to Armenia and it was done. All regulatory documents issued by the EUEC and adopted by the Board required further adoption by the Commission.

4.2. Descriptive analysis of food supplements regulatory environment in 2008–2012

According to European Food Safety Authority (EFSA) food supplements are concentrated sources of nutrients (i.e. mineral and vitamins) or other substances with a nutritional or physiological effect that are marketed in "dose" form (e.g. pills, tablets, capsules, liquids in measured doses) (European Food Safety Authority, 2020).

The Russian legislation defines food supplements as biologically active food additives which are compositions of natural or identical to natural biologically active substances intended for direct intake with food or incorporation into food products in order to enrich the diet with individual food or biologically active substances and their complexes. Though the definitions differ between legislations the meaning remains the same.

The key legislative acts regulating FS turnover in the Russian Federation during 2008 till 2011 were following: The Federal Law "On the Sanitary and Epidemiological Well-Being of the Population" of March 30, 1999, No. 52-FZ (State Duma, 1999) particularly article 42 "Sanitary and epidemiological examinations" and article 43 "State registration of substances and products".

Other acts in power – Federal Law "On the Quality and Safety of Food Products" No. 29-FZ (Государственная Дума, 1999a). SanPiN 2.3.2.1290-03 "Hygienic requirements

for the organization of production and turnover of biologically active food additives" (Главный государственный санитарный врач, 2003); MUK 2.3.2.721-98 "Determination of the safety and effectiveness of biologically active food additives" (Институт питания РАМН, 1999); Guidance R 4.1.1672-03 "Guidance on methods for controlling the quality and safety of dietary supplements" (ГУ НИИ питания РАМН, 2003). In 2011 the additional legislation of Eurasian Union came into force, namely "Unified sanitary and epidemiological and hygienic requirements for goods subject to sanitary and epidemiological surveillance (control)" as amended by the Decision of the Commission of the Customs Union of April 7, 2011 No. 622 with all appendices and changes (Комиссия таможенного союза, 2010).

The authority "Federal Centre for Hygiene and Epidemiology" of Rospotrebnadzor pursuant to clause 1 of the Order of the Chief State Sanitary Doctor of the Russian Federation of 2006 No. 36 "On state registration of biologically active food supplements" (Роспотребнадзор, 2006) carried out a sanitary and epidemiological examination for the purpose of state registration of biologically active food additives (Lozda, 2019).

According to the Decision of the Commission of the Customs Union (CU), in 2010, a list of documents required for the sanitary and epidemiological examination of biologically active food additives manufactured in the customs territory and beyond was approved. Thus, there were significant legislative changes also in the regulatory environment of FS making common trends similar to pharmaceuticals; however, practical implications of the CU legislation became significant after 2012 (Комиссия таможенного союза, 2010).

According common CU regulations sanitary and epidemiological examinations was carried out in accordance with the procedure, which included the requirements for the provision of a registration dossier of FS from the moment it is submitted by the applicant to the receipt of expert opinions. According to these regulations, the dossier was accepted, and initial examination was carried out. In the course of this examination, the necessary laboratory studies were determined by sanitary-hygienic indicators (safety) and the content of biologically active substances (authenticity).

In accordance with the Decree of the Government of the Russian Federation dated December 21, 2000 No. 988 "On state registration of new food products, materials and products", information on registered FS was entered in the State Register of food products that have passed state registration (Прав. Рос. Федерации, 2000).

Thus, the legal pathways of FS marketing authorization followed key general steps of pharmaceuticals such as safety and quality examinations.

Overall, FS must undergo mandatory state registration and has to obtain an appropriate certificate prior to sale in Russia in order to initiate the free trade. However, conclusions

about the efficacy of FS and the claims of positive effects on the human body remained outside of the state registration process. That somehow mimicked indications for medicines. Therefore, the certificate of state registration of food supplements had no information about the efficacy of FS. For the purpose of advertising in the media, a manufacturer might submit information about features of a product, including composition, properties, effects on human health, and conditions of use according to the instruction of use as approved during the state registration. The legislation regulating the labelling of FS required that the information for consumers complies with regulations of paragraph 4.4 of Sanitary Rules and Regulations or so-called SanPiN 2.3.2.1290-03 "Hygienic requirements for the organization of production and turnover of biologically active food additives" (Главный государственный санитарный врач, 2003). The information on the label must correspond to the information agreed upon during the state registration (sanitary epidemiological examination) and described in the Certificate of State Registration. Otherwise, according to paragraph 7.4.6 of SanPiN 2.3.2.1290-03, the use of noncompliant dietary supplements is not permitted (Главный государственный санитарный врач, 2003).

To prevent consumers from engaging in misleading advertising and subsequent legal consequences for the manufacturers, the voluntary certification system (VCS) had been established. VCS was an official system that applied to goods, services, or equipment if their quality assurance was not a mandatory requirement of the law. VCS was regulated by legislation. This form of confirmation of compliance was usually carried out at the request of a manufacturer, a seller of the goods, or a customer. For example, large retail chains wanted to see documentary evidence of quality when purchasing a product, even if safety assessment of the product is not required. The same applied when a manufacturer intended to put health claims on the label of FS. In this case, voluntary certification of the products was conducted. The products were tested with regard to the claims and a voluntary certificate of conformity (VCC) was issued. In the past, numerous VCSs have been established or registered to provide services related to FS. The schemes of certification, timelines, prices, and outcomes that they offer differed. Taking into account a significant amount of institutions and occasional controversial information available, making a selection of an authority for application for certification involved a complicated decision (Lozda, 2019).

As seen from the figure below, before the voluntary certification (VC) a FS had to have a valid State Registration Certificate. After the VCS was chosen and an Application submitted the laboratory testing and evaluation of the claims was performed simultaneously.

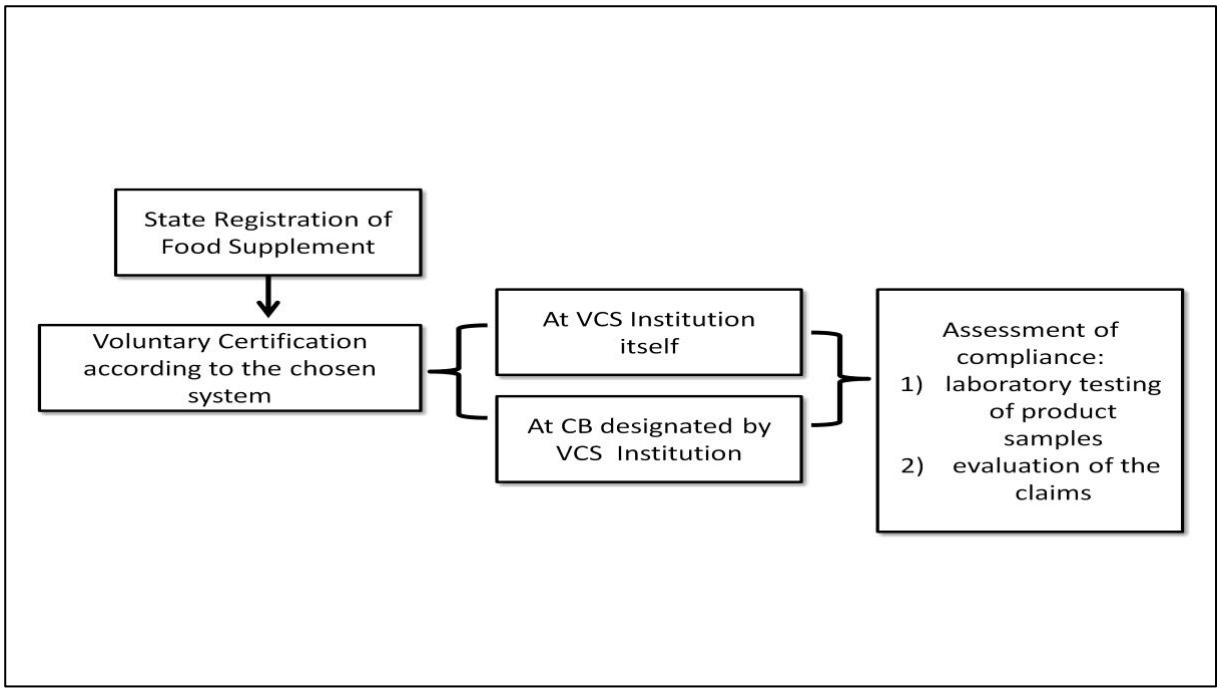


Figure 4.6. A flow chart showing the chronological order of filing

4.2.1. The System of Voluntary Certification of FS in the RF

The framework of the VCS was governed by Federal Law No. 184-FZ of December 27, 2002, "On Technical Regulation" (Государственная Дума, 2002b). A VC was carried out at the initiative of an applicant according to the terms of an agreement between the applicant and the certification body (CB) to establish compliance with national standards, standards of organizations, VCSs, and contract terms. The subjects of voluntary certification could be products, production, operation, storage, transportation, sale and disposal, work and services, and other facilities for which standards and voluntary certification systems have established requirements. VCSs could be created by a legal entity and (or) an individual entrepreneur or several legal entities and (or) individual entrepreneurs. A person or persons who created a VCS established a list of objects that were the subject of certification, their compliance characteristics for voluntary certification, the rules of voluntary certification process provided by this system and the service fees. The VCS issued a conformity mark. The framework of a VCS was expected to confirm the quality of the products and evaluate the efficacy of the use of FS to optimize various types of metabolism and normalize and/or improve the functional state of organs and systems of the human body according to SanPiN 2.3.2.1290-033.3 Thus, a VCS confirmed the efficacy and conformity of the properties of the products declared by a producer or importer, protected consumer rights with regard to the purchase of the products of inadequate quality that could be dangerous for life and health, and

allowed the producer to inform the consumers not only about the safety of the products and the contents of biologically active components of FS but also on its efficacy according to the claimed properties. The claims for a particular FS were tested according to manufacturer instructions. The parameters checked in a sample of a product included compliance with a set of technical standards (GOST) or technical specifications. Thus, laboratory testing, and other trials performed during the VCS procedures permitted the manufacturer to confirm the quality of provided goods and certifies compliance with the requirements specified in the regulatory documents. In other words, VCS of FS confirmed the quality of a product and compliance of FS with legal requirements. Therefore, VCS involved 2 significant evaluation steps. One step was laboratory testing of product samples with regard to claimed composition, and another step was evaluation of the claims. The chronological order of filing is shown in Figure 4.6. According to the legislation, VC did not require mandatory involvement of state institutions. Some misleading information was circulating around stating that some voluntary certificates issued by the state institutions have superiority over other certificates. According to the legislation, all VCSs had the same legal power. Moreover, VCS did not require state approval. Paragraph 3 of Article 21 of Law No. 184-FZ (Государственная Дума, 2002b) stated that a VCS can be registered; according to literal interpretation of the law, an option without state registration is permissible. This situation did not make it easier to distinguish between a wide variety of institutions handling VC. Finally, everything depended on the reputation of these institutions and willingness to register their VCS. According to the Government Regulation No. 294 of June 17, 2004 (Прав. Рос. Федерации, 2004), Rosstandart maintained a unified register (UR) of registered voluntary certification systems (Lozda, 2019). Thus, VCSs dealing with FS could be registered at Rosstandart and could be found in the UR database. This approach was followed by reputable institutions. A specific issue related to VCSs was that institutions that participated in VC could have various specializations and performed various functions. VCS differed from mandatory certification because the Federal Service for Accreditation (Rosakkreditatsiya) or Rosstandart did not implement the policy, rules of operation, and accreditation; however, as a rule, a VCS institution on its own represents the focal point of the system. For example, activities related to approval of compliance of the products or services with GOSTs, specifications, and technical regulations might be performed only by authorized (accredited) subjects, Certified Bodies (CBs), who must have a document confirming the activity at the legislative level. An accreditation certificate (AC) was the document required in Russia. AC of a certification body was a document issued by an authorized body; it certified the competence of a legal entity when issuing certificates and declarations for certain types of products or services. According to the Resolution of the

Government of the Russian Federation No. 845 of October 17, 2011, “About the Federal Service for Accreditation” (Прав. Рос. Федерации, 2011), the functions of accreditation of legal entities and individual entrepreneurs in the national accreditation system and the formation and maintenance of the register of accredited subjects were performed by Rosakkreditatsiya. Until 2012, ACs were issued by Rosstandart. AC was issued for a period of 5 years. Relevant sections of the website of the Federal Accreditation Service contained searchable information about the status of a CB and about the area of its accreditation. The certificate of accreditation of CB was a document with its own established standard with the requirements as specified in Order No. 295 of the Ministry of Economic Development of the Russian Federation of May 26, 2014, “On Approval of the Form of the Certificate of Accreditation” (Минэкономразвития, 2014); (Минэкономразвития, 2019). The certificate also contained an alphanumeric code, 2 letters and 2 digits, unique for each CB. However, AC issued by Federal Accreditation Service was not mandatory for VCSs. Accreditation of CBs in Rosakkreditatsiya was required for the mandatory certification systems. In the case of VCSs, Rosakkreditatsiya and Rosstandart only maintained a register of certification systems, but the registration there was voluntary. Additionally, CB could be accredited in several certification systems, and a certification system itself may have sectorial specialization; in these cases, a client may choose a certification system after a consultation with the experts. However, the absence of a selected system from the register of the certification systems did not mean that the law had been violated, because the law did not require registration in the registry. The only difference between registered and unregistered systems was that the transactions with the former could be usually conducted with a greater confidence. It could be important only if a CB was accredited to assess compliance with Rosakkreditatsiya (Lozda, 2019).

4.2.2. VCS Certification Bodies

Activities related to the approval of conformity of products or services to standards, specifications, and technical regulations might be performed only by authorized (accredited) subjects, that is, the CBs, which must have a document confirming their activity at the legislative level. An example of this type of document in Russia was an AC, as mentioned earlier in the text. Accreditation of a CB by a VCS itself was a unique feature of VCS. Accreditation by VCS involved verification of CB compliance with the rules and requirements of a particular system; after that, the organization was permitted to function using the methods and brand of the VCS that have performed the accreditation. The institutional functions within VCS are described in Figure 4.7.

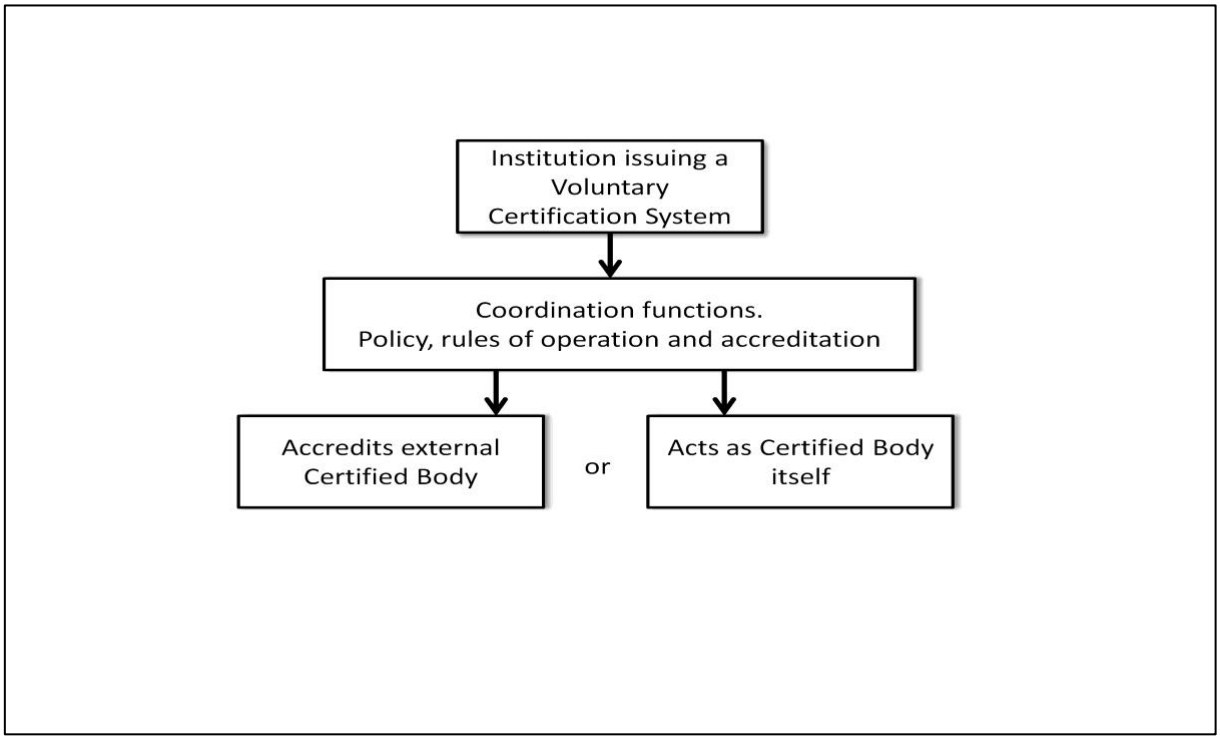


Figure 4.7. A scheme of institutional functions within VCS

For example, there was a state institution called Rospotrebnadzor (Lozda, 2019). A Rospotrebnadzor subordinate institution, "Centre for Hygienic Education of the Population" (CHEP), had been registered at Rosstandart, a VCS: "The system of voluntary certification of biologically active food additives." However, CHEP itself did not perform VC. It had accredited 2 different private CBs to perform a certification within that particular VCS. Both CBs had an AC issued by CHEP. This is an example of a VCS created by a state institution that accredited private CBs. In this case, the VCS founder was a state company, but the CB was private. It is worth mentioning that some ministries and government departments had their own VCSs and fulfilled their role as a focal point. Historically, collisions around mandatory certification systems were frequent when an entrepreneur was essentially forced to pass certification in these systems. Now, mandatory certification was carried out only in a single system, namely, GOST R, and the accreditation function was focused in Rosakkreditatsiya; other powers were distributed between Rosstandart and a number of other institutions. In the case of VCSs, the registration at Rosstandart and Rosakkreditatsiya was voluntary. Thus, there was no superiority of one VCS over another in terms of legal power. Moreover, even unregistered systems did not lose their right to develop and use their certification marks. A private company "Certification and training centre for biocorrectors" (CTCB) was an example of one of the oldest Rosstandart-registered VCS called "Effective

Biocorrectors". In this case, CTCB itself was also a CB. CTCB had full legal rights to certify FS and use a certification mark since 2004. Voluntary certification of FS could be performed all over Russian Federation. CBs were located not only in Moscow. For example, there is "Siberian Federal Centre for Health Nutrition" located in Novosibirsk that has a Rosstandartregistered VCS called "Healthy Nutrition–Health of the Nation". The certificate issued in Novosibirsk was also valid within the whole territory of the country. Critical differences between VCSs and CBs were in specific procedures that were conducted during the assessment of compliance as reflected in the VC schemes. The schemes could vary but there was a generic difference versus mandatory certification. According to the Federal Law No. 184-FZ (Государственная Дума, 2002b), processing of a voluntary conformity assessment was initiated by an applicant in a CB, while VCSs focused on demonstration of positive qualities of a particular FS producer. The coordination of certification schemes was negotiable between a CB and a customer. The customer was also free to choose regulatory documents, contracts, and even specific clauses of these documents, and their conformity will be certified by CBs. Thus, evaluation of FS conformity toward a particular regulatory ND was an essential difference between CBs. Therefore, the CB paid particular attention to certification as a marketing tool including advertising and the use of marking signs. In some cases, the certification was particularly emphasizing the advantages so that the customer of the certification service can attract the clients. Therefore, CBs were mainly focused on the product control phase. In summary, CBs differed with regard to ND used as a basis of conformity assessment, claims and advantages so that the customer can attract the client, the validity term of the issued certificate, and financial conditions of each VC.

4.2.3. The Certification Schemes and Outcomes

In Russian Federation, any certification process, be it voluntary or mandatory, could be conducted in two parallel systems of conformity assurance. These systems included the System of GOST R and Certification System on Technical Regulations of the Customs Union (TRCU). In the first case, the quality assurance procedure ensured compliance with the Russian State Standards and Standards of the Industry (OST). In the second case, compliance was verified according to TRCU. Consequently, each of these systems had its schemes of certification of goods and services. There was a total of nine various schemes in the GOST R system that can be used depending on the type of object and the assessed standard of compliance. According to the principle of application, certification schemes could be divided into three main groups described in the following table.

Table 4.3.

Certification schemes in Russian Federation

Certification scheme	Description	Coordinating Institution	
		Voluntary certification	**Mandatory Certification**
For a batch	When using this scheme, certification is carried out in relation to a particular batch of products, indicating the quantity of goods in the batch in the certificate. In this case, the certificate will only apply to those units that are declared in the certificate. Most often this scheme is used for importing of equipment. It can also be used for the certification of domestic goods.	VCS institution	Rosakkreditatsiya or Rosstandart
For a contract	This scheme is used for certification of imported products. The certificates indicate the recipient (the Russian company) and the manufacturer, as well as the number and date of the contract for which the product is delivered as the link. With this certification scheme, a certificate can be issued from one year to three years.	VCS institution	Rosakkreditatsiya or Rosstandart
For a Serial Release	This scheme is used for certification of serially produced products. Under this scheme, both domestic and imported products are certified. One company is indicated as the recipient and manufacturer. The certificate is also issued for a period of one to three years. The recipient in this case may be a Russian manufacturer or a foreign company.	VCS institution	Rosakkreditatsiya or Rosstandart

In the TRCU system, principles were very similar but there are certain specific features.

A critical difference is that only a Russian company or an organization registered in one of the countries of the Customs Union could receive the certificates of the Customs Union. Companies that were not residents of Russian Federation or one of the countries of the Customs Union cannot be certified. For example, a foreign producer which would such as to have a VC in its own name could obtain certification only within the GOST R scheme. A locally authorized representative was required to obtain a VC within TRCU.

Thus, the certification schemes according to GOST R/OST or TRCU distinguished between various CBs. Any CB within VCS had its own procedures/schemes to follow either the GOST R/OST or TRCU schemes, and the procedures were explained to the client during the initial contact.

Another critical issue from the client point of view was the standard or technical regulation considered for checking the FS compliance. CBs using the TRCU scheme applied Technical Regulation of Customs Union number TR TS 022/2011 “Food products regarding labelling” (Комиссия таможенного союза, 2018) and number TR TS - 021 – 2011 “On food safety” in the majority of cases (Комиссия таможенного союза, 2019). A typical pathway to VC in compliance with TR TS 022/2011 and TR TS - 021 – 2011 could be used according to one of the following schemes.

Scheme 1: to confirm the quality and uniformity of the products during the validity period of the certificate. When applying this scheme, testing of the samples of various series selected from the manufacturer is performed in the testing laboratories determined by CB. The product conformity certificate is valid for 6 months.

Scheme 2: to confirm the quality and uniformity of the products during the validity period of the certificate including an inspection of a production site. This scheme also assumes testing of samples of various selected batches from the manufacturer and an inspection of a production site at least once a year or at least twice during the validity period of the certificate by the experts appointed by CB.

In this case, VCC was valid for 12 months.

Scheme 3: to confirm the quality of a particular batch of a product assuming laboratory testing of the product samples. Effective period of VCC does not exceed the expiration date of the relevant product lot (Lozda, 2019).

In addition to VCC, the client had the right to use a conformity mark that can be printed or used as a sticker depending on the scheme.

All these schemes assumed minimal expiration date of VCC leading to frequent renewals and potentially costly manufacturing site inspection.

It should be noted that if FS was certified according to TR TS 022/2011 and TR TS - 021 – 2011, approval of the general function claims for FS use indicated on the label was implied. Sometimes, it was quite confusing because reports confirming clinical efficacy of FS, which were issued by organizations and institutions authorized to conduct clinical studies of FS, were requested along with other documents supplied to CB during the VC process. These reports were issued on the basis of real clinical trials performed with a particular FS. However, the approved claims could not contain an evidence of clinical efficacy because the

standards did not assume such type of evaluation. For example, if an immunostimulatory FS was clinically tested to relieve some cold symptoms, the trial outcome with regard to efficacy cannot be used to describe a relief of symptoms. Thus, for example, a statement "helps to release nasal congestion and breathe more freely" had be replaced with more diplomatic statement such as "maintains free flow through the airways". Thus, TR TS 022/2011 and TR TS - 021 – 2011 compliance of VC was less geared to prove clinical efficacy of a FS.

On the other hand, VCS could be based on the GOST R/OST scheme and Industry Standard OST 42-511-99 "Rules for conducting qualitative clinical trials in the Russian Federation" (Минздрав, 1998) in particular. Non-medicinal health-improving products were the subjects of this system including FS, specialized food products, and cosmetics if not registered as a medicine. This system was more suitable for justification of clinical efficacy of FS and had rather simple scheme of obtaining VCC. Briefly, the whole procedure was as follows. An applicant performs a clinical trial with a particular FS and laboratory testing of a product and then, submits the results to CB. CB evaluates these documents and issues a VCC in the case of a positive outcome. The VCC is valid for an indefinite time, and a conformity mark can be used to avoid frequent renewals. In the case of OST 42-511-99-based (Минздрав, 1998) VCS, immunostimulant from the example described in the preceding paragraph would be approved with the claim "helps to release nasal congestion and breathe more freely".

There was no unambiguous answer regarding a specific list of documents required from an entrepreneur when applying to CB to confirm compliance with a chosen standard. In each CB case, the list of required documents varied. This was closely linked to the idea of VCS. Each VCS had an original procedure and rules of certification.

4.2.4. Food supplements regulatory environment from 2008 till 2012 overall conclusions

As seen from above mentioned chapter 4.2 , the scheme of FS marketing authorization and VCS acknowledges suitability for that environment to be used as a control model to evaluate the performance of pharmaceutical legislation changes which took place in 2010. Further, in statistical analysis chapters of the present theses related to legislation performance, particularly parallel trends assumption, we can see that the number of registered products follow the same trends before the adoption. The introduction of CU legislation followed by implementation in late 2011 maintained the growth tendency of registered FS.

4.3. Descriptive analysis of Pharmacovigilance system in the RF till 2013

In 1997 the Federal Centre for the surveillance of side effects (SE) / adverse drug reactions of pharmaceuticals of the Ministry of Health of the Russian Federation and several regional centres of the same purposes were organized. Simultaneously a database of SEs, received as spontaneous messages, began to be created. A year later, the Federal Centre was transformed into the Scientific and Practical Centre for the Control of Side Effects of Medicines, and later a series of renaming and transformations of this structure followed. For the first time, the obligation of medical practitioners to monitor SEs was enforced by the Federal Law "On Medicines" of 1998 (Федеральный закон, 1998). However, the system for collecting information on SEs did not function sufficiently due to the low problem awareness by medics. A new development stage of the pharmacovigilance system begun in 2007, when the Federal Centre for Monitoring the Safety of Medicines (FCMSM) was organized as a structure of the of Roszdravnadzor, namely Federal State Budgetary Institution Scientific Centre for Expertise of Medical Medicines. This Centre fulfilled the functions of monitoring the safety of drugs, and also conducted an expert assessment of the facts and circumstances of the development of SEs.

Since 2008, the active launch of regional drug safety monitoring started. At that time, Roszdravnadzor began intensive regulatory activity by issuing a number of recommendation letters on how to organize the pharmacovigilance system in medical institutions. Then it was proposed to introduce a notification form for SEs; this form was posted on the official website of Roszdravnadzor (Росздравнадзор, 2008a). Another important, but not completely implemented, step was Roszdravnadzor Information Letter No. 01I-518/08 of 08/15/2008 (Росздравнадзор, 2008b), which recommended all medical institutions to appoint persons responsible for monitoring the efficacy and safety of drugs and introduce the SE registration form "Notification of medicines adverse effects" to be put in each medical history and outpatient card with mandatory filling, regardless of whether the SE was registered or not. The procedure was not fully implemented and only a few hospitals adhered to these recommendations. Additionally, all these letters were later withdrawn by Roszdravnadzor itself. However, despite the somewhat successful activities of regional drug safety monitoring centres that conducted active outreach, identifying drug safety problems locally level and, their actions were actually suspended by another letter of Roszdravnadzor. From that moment, the functions for monitoring drug safety became centralized.

Thus, the pharmacovigilance system's evaluation as a centralized State process can be assumed to begin in 2009 that is an important fact for the parallel trend assumption for statistical calculations described further.

The crucial changes in the pharmacovigilance system have begun with the adoption in 2010 of the NPL. In accordance with the Law, healthcare entities were obliged to report to Roszdravnadzor all cases of SEs not specified in the instructions for the use of drugs. They were obliged to report also serious adverse reactions (SAE), unexpected adverse reactions, and drug interactions that were identified during clinical studies and the use of drugs.

The procedure of drug safety monitoring was described in detail by Order of the Ministry of Health and Social Development No. 757 of 08/26/10 (Минздравсоцразвития, 2010). Then an automated information system was created by Roszdravnadzor, either. The system became a centralized pharmacovigilance database in Russia.

According to the NPL, all subjects of drug circulation such as doctors, pharmaceutical workers, patients, and consumers of drugs, legal entities – manufacturers of drugs, MAHs, legal healthcare entities become sources of spontaneous messages.

4.3.1. EAEU impact on pharmacovigilance system in the RF

According to the Article 12 of the MCA Member States shall ensure the efficient functioning of the national pharmacovigilance systems. It has to be in agreement with good practice of pharmacovigilance, approved by the Eurasian Economic Commission (ЕЭК, 2016h), and the law of the MS. Member States shall establish in its legislation provisions concerning the liability of MAHs violating the mandatory requirements in the field of pharmacovigilance. Contrary to the draft MCA where the creation of a single supranational body – the Pharmaceutical Inspectorate was proposed at the moment the competent authorities of the MS will provide the monitoring of MAH activities regarding PV following good practices and pharmacovigilance legislation of the MS. Hence interaction of pharma industry and State Authorities will remain the same as per national circumstances. The information exchange among the competent authorities of the MS regarding identified adverse reactions, assessment of the risk/benefit ratio of medicines circulating in the territories and measures to be taken in excess of the risk is governed by the procedure approved by the EUEC in the good pharmacovigilance practice of Eurasian Economic Union (EUGVP) (ЕЭК, 2016h). The competent authorities (CA) of the MS will provide the Monitoring of Implementation by MAHs all pharmacovigilance obligations under the EUGVP. The information exchange between the CA of the MS related to identified adverse

reactions, changes in the assessment of the risk/benefit ratio and measures taken will be made according to Complete technological documents to the overall process. The process envisages the formation, maintenance and use of a single database of information on the identified adverse reactions (actions) of medicines, including the reports of the ineffectiveness of drugs (Lozda, 2017a). MS shall exchange information on the results of inspections of the pharmacovigilance system of the MAHs to determine their compliance with the national laws. Thus, there are several common Eurasian Union documents related to pharmacovigilance prepared which defines principles and information turnover among MS as well as requires national legislation unification. It seems quite a challenging process for market operators to identify similarities and differences amid MS and EAEU requirements to be prepared for coming changes.

4.3.2. PV requirements in the RF after 2013

According to the Federal Law No. 61-FZ from 1st of July 2015, the MAH was recognized as the person responsible for the quality, safety, and efficacy of the drug. The MAH is in charge of monitoring the effectiveness and safety of the drug and must make the records of such monitoring to the by the Roszdravnadzor within defined intervals (Lozda, 2017a).

All parties participating in circulation of medicines were obliged to report all cases of the collateral actions which haven't been specified in the pharmaceutical product information, the serious adverse reactions, unexpected adverse events, and features of interaction with other medicines which were revealed during clinical research and clinical application of medicine (Lozda, 2017a).

Failure to comply with PV measures to ensure the safety of drugs could even lead to the termination of state registration of the pharmaceutical by the decision of the Ministry of Health. The Safety Terminology in Russian was consistent with The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use terminology.

The general guidelines on pharmacovigilance had been approved by the Ministry of Health Order No. 757n of 26 August 2010 (Министерство здравоохранения и социального развития, 2010b). The MAH was responsible for monitoring pharmaceuticals' efficacy and safety and must make the records of such monitoring to the authorized state body within defined intervals. The monitoring of the safety of medicines was carried out by the Federal Service of Surveillance in Healthcare (Roszdravnadzor) which establishes the appropriate

procedure. A failure to comply with PV measures could lead to the termination of state registration of the pharmaceutical by the decision of the Ministry of Health.

To harmonize national PV requirements with the EUGVP and Good Clinical Practice of the Eurasian Economic Union, Roszdravnadzor finalized description of pharmacovigilance procedures in the appropriate legislative act the Order No. 1071 On Approval of the Procedure for the Implementation of Pharmacovigilance (Росздравнадзор, 2017) at the end of February 2017. Thus, drug safety monitoring carried out by Roszdravnadzor based on messages issued by subjects of circulation of medicinal products, Periodic Safety Update Reports (PSUR) issued by MAHs and information obtained during the implementation of the State control (Lozda, 2017a).

4.3.3. Safety reporting requirements in the RF after 2013

According to the Order 1071 (Росздравнадзор, 2017) reporting requirements were identical to ones described in the document "On approval of rules of good pharmacovigilance practice of Eurasian Economic Union" (EUGVP) (ЕЭК, 2016h). The adverse reaction terminology referred to the EUGVP. The expedited case reporting concerned to serious adverse reactions (AD) occurred in Russia and serious unexpected adverse reactions found in the territories of other states. Any safety information from other observations that could change the risk-benefit evaluation to be provided in an expedited manner is the same as per EUGVP.

Besides expedited cases mentioned in the EUGVP some additional situations had to be reported within 15 days period: 1) cases of transmission of an infectious disease through a medicinal product; 2) cases of lack of declared efficacy of drugs used in conditions that pose a threat to human life, vaccines for the prevention of infectious diseases, drugs to prevent pregnancy. Situations when the lack of clinical effect is not due to the individual characteristics of the patient and (or) the specificity of his disease; undesirable reactions resulting from the abuse of the drug in cases of deliberate drug overdose, with exposure to occupational activities, or in cases of intentionally harmful use for human life and health.

The case reports on serious adverse reactions with fatal or life-threating outcomes had to be sent to the Roszdravnadzor within 3 days. The cases of individual intolerance to medicines, which are prescribed under the trade name within programs of preferential drug provision must be reported within 5 days from the date of issuance of the relevant prescription.

All above mentioned reports had to be sent to Roszdravnadzor as “Notice of adverse reaction or lack of therapeutic effect of the drug” according to Appendix No. 1 the Order. The Notices were sent to Roszdravnadzor through the Automated Information System of Roszdravnadzor (AIS) “Pharmacovigilance”.

The AIS was created for the collection and analysis of information on side effects and other drug-related safety issues. The system was devoted to the staff of the central apparatus of Roszdravnadzor, its regional bodies, expert organizations, employees of regional centres for drug monitoring, health care professionals as well as authorised persons of pharmacovigilance (APP) of pharmaceutical companies. Following the letter of 02.12.2008 Roszdravnadzor No. 752/08 (Росздравнадзор, 2008c) to gather access to the electronic system (Lozda, 2017a).

4.3.4. Periodic Safety Update Report submission requirements in the RF after 2013

According to the Order 1071 (Росздравнадзор, 2017), a procedure for calculating the date when the MAH ends the collection of safety information for the next PSUR and the frequency of its submission for various international non-proprietary names or group names was approved by Roszdravnadzor. For medicinal products whose international non-proprietary name or group name was not included in the approval list, the frequency and timeline of submission were counted from the date of the first state registration in the world and was as follows:

a) every 6 months from the time of the first state registration in the world for the first 2 years;
b) annually for the next 2 years;
c) further – every 3 years. The submission conditions are identical to ones mentioned in the EUGVP (ЕЭК, 2016h). The PSURs are submitted to Roszdravnadzor through AIS or on electronic media. The format and language requirements as per EUGVP (Lozda, 2017a).

4.3.5. PV requirements of the EAEU

In 2016 only some clauses of section 7 and full section 4 of the EUGPV – Inspection of the pharmacovigilance system were in force (ЕЭК, 2016h). The entire document will become operational after ten calendar days from the date of entry into force of the MCA. The principles of EUGVP complied with requirements of European Medicines Agency EMA

Guideline on good pharmacovigilance practices (GVP) (European Medicines Agency, 2017b). Following conditions were intended to be mandatory for MAHs:

a) the MAH must develop and implement a pharmacovigilance system to monitor one or more medicinal products;
b) the MAH is responsible for creating and maintaining a master file for the pharmacovigilance system;
c) the MAH is required to designate an APP in the MS having necessary qualifications to be responsible for the establishment and operation of the pharmacovigilance system described in the master file of the pharmacovigilance system (Lozda, 2017a).

The terms utilised in the EUGVP were similar to European ones and are described in table 3 of Supplements. The reporting timeline for above mentioned is within 15 calendar days from the date of receipt by the MAH or his authorized representative appropriate information. The report shall be submitted to the CA of the MS. Individual case reports should be presented to the CA of the MS electronically. The format of individual reports should be in agreement with the one set by the International Conference on the Harmonization of Technical Requirements for Medicines for Medical Use (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) (European Medicines Agency, 2017a). Other expedited safety information has to be submitted in writing to the CA of the MS where medicine is registered (Lozda, 2017a).

4.4. Regulatory performance analysis of NPL impact on institutions issuing medicines MA in the RF

During the present study, we found that the number of registered medicines and authorizations issued per year significantly decreased during the introduction of NPL. Thus, the expertise and ethical review of the possibility of clinical studies of the drug, as well as the implementation of CT, took more time. Interestingly, according to the Association of Clinical Trials organizations (ACTO) the total time for obtaining a permit for CT and permits for import / export of investigational product was an average 135 calendar days in 2012 (АОКИ, 2013), which is less compared to 164 calendar days reported in 2011. The table below shows the time as mentioned above during the period from 2007 to 2012.

Table 4.4.

Total time to obtain CT and drug import permit

Year	2007	2008	2009	2010 Jan-Aug	2011	2012
Average number of calendar days necessary to obtain CT permit + import/export permit	122,6	110,7	107,5	112,1	164	135

An interesting fact is seen in the year 2010, where CT permit statistics are given from January to August only. The explanation is that the introduction of NPL also led to considerable administrative changes in the authorities performing the entire process of MA of pharmaceuticals. Before NPL, the executive functions of pharmaceutical registration were provided by Roszdravnadzor. The flowchart for obtaining CT permission and medicine MA before the introduction of the NPL is shown in the figures below.

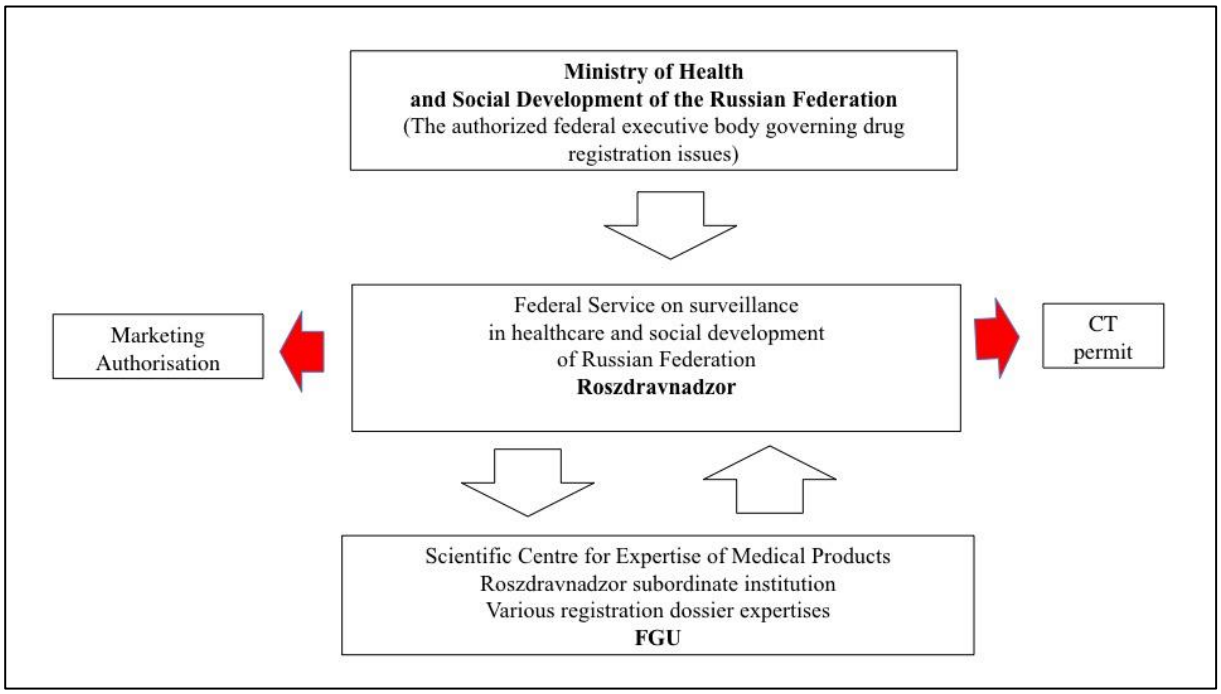


Figure 4.8. MA and CT issue scheme before NPL

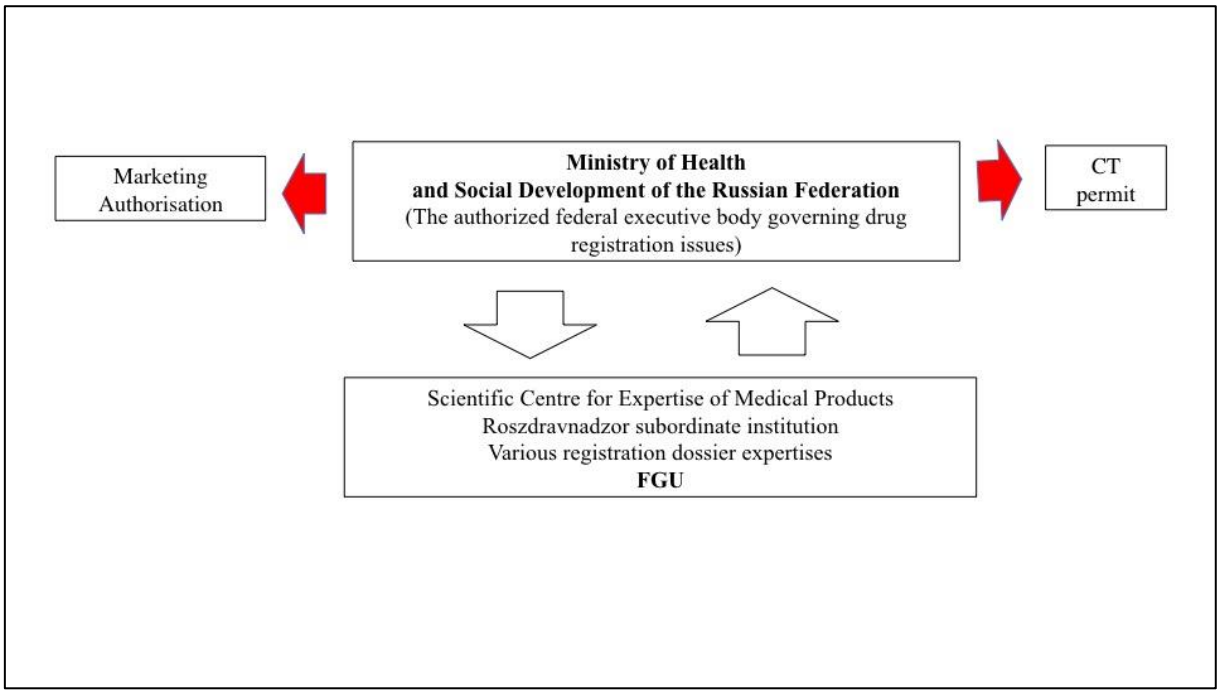


Figure 4.9. MA and CT issue scheme after NPL

The above-mentioned figures show the general subordination of the involved institutions before and after the introduction of the NPL. The Roszdravnadzor issued both MAs and CT permissions, and FGU made evaluations of submitted applications before 2010. After the introduction of NPL, another legislative act the order of the Government of the RF of 4 August 2010 N 1316-r (Прав. Рос. Федерации, 2010) was introduced. According to this order, the Government assigned FGU to the direct subordination of the Ministry of Health and Social Development of Russia from former supervision by Roszdravnadzor. In addition, the Roszdravnadzor itself lost any involvement in the MAs of CT. Thus, at the end of 2010, two crucial institutions taking care of provisions of medicine access were reorganized or excluded from the process. The MHSD was given a 3-month time period to finish reorganizational issues. From the ACTO data (АОКИ, 2010), we see that from August till the end of 2010, at least CT permits were not issued.

To evaluate the impact of structural reforms on NPL performance, we carried out the function efficacy assessment of institutions involved in MA by statistically comparing them with a control unit. The approach of legislation performance evaluation mentioned in literature is to compare items of interest with control units from different companion jurisdictions (in a territorial sense). Unfortunately, by comparing the Russian drug, MA authorities with companions in the EU would not encounter national specific issues. Therefore, as a suitable control unit, we chose FS authorizations issuing authorities. Thus, in

the previous chapter 4.2 FS legislation pathways are discussed in detail. The assumptions in favour of our choice are as follows.

a) both FS and pharmaceutical prior marketing access in Russia require registration;

b) The safety and quality of the products are assessed. In the case of VC, producers are required to prove their health claims by clinical efficacy testing, which mimics CTs for drugs.

c) Most importantly, during the observational period of the present study, FS registration and MA of medicines were carried out under supervision of the same ministry.

The registration pathway comparison between FS and drugs is shown in the pictures below.

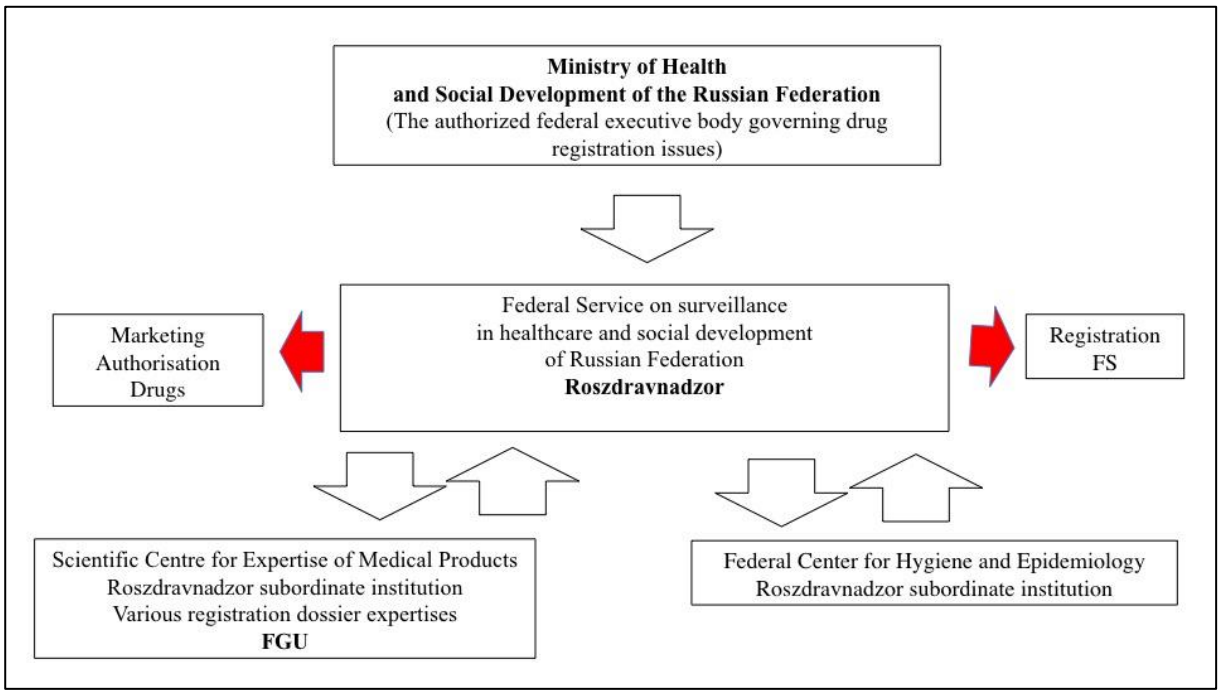


Figure 4.10. MA and FS registration issue scheme before NPL

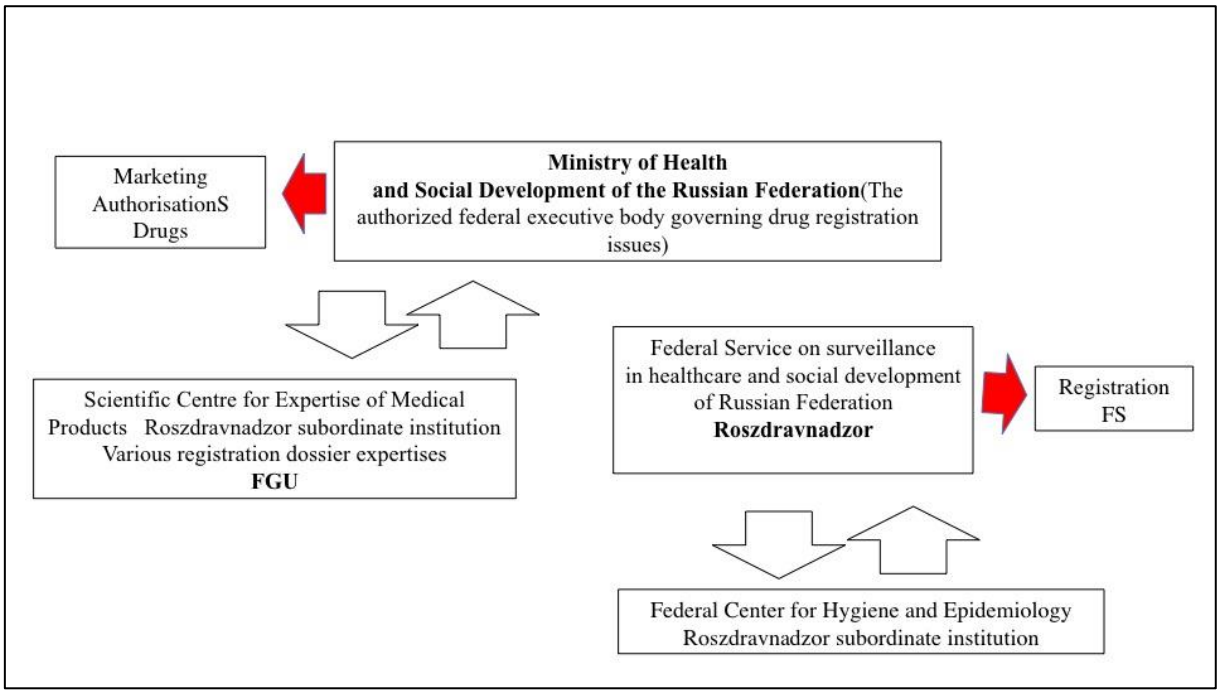


Figure 4.11. MA and FS registration issue scheme after NPL

As seen from the schemes above, the administration of MA changed, whereas FS remained the same as seen in the schemes above. Regarding registration procedures and requirements during the observational period, FS did not face any legislative changes until late 2012 when EAEU norms were introduced, but that did not influence registration pathways in Russia.

Generally, in the same jurisdiction, there are two institutions performing licensing with and without administrative changes. Therefore, we assumed that both would be comparable to assess their performance due to organizational changes.

4.4.1. Parallel trend assumption for medicines and FS prior NPL

In the state institution performance assessment under NPL, we evaluated two efficacy indicators: the number of registered medicines and issued medicine MAs per year vs. the same for FS.

Thus, the treatment (impacted by legislation – NPL) unrelated to an outcome at baseline (allocation of the intervention was not determined by outcome) as a FS and pharmaceutical MA systems do not interfere.

Treatment and control groups comparing the quantity of registered medicines as seen from the trend lines in Figure 4.12. could be considered as being parallel in the outcomes prior to the intervention.

The literature data show that there was a steady increase in the number of medicine names due to active MA efforts in the Russian pharmaceutical market, and in 2009, it reached 10,790 units (Яворский, 2010).

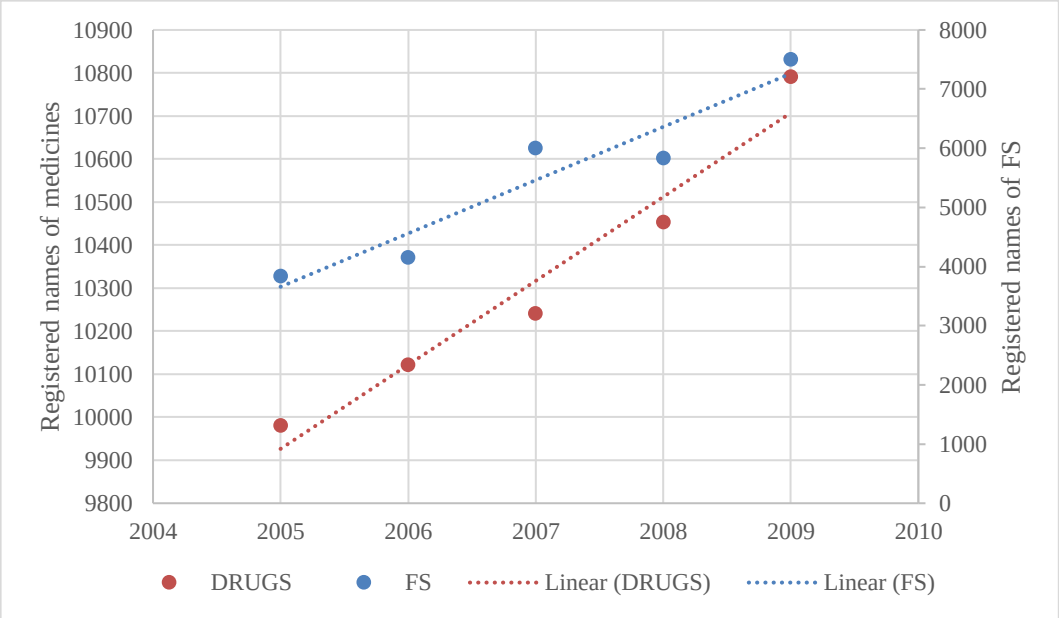


Figure 4.12. Quantity of names of registered medicines and food supplements prior NPL

The numbers of registered FS were derived from other literature data (Пронченко, 2010). According to Figure 4.12. the composition of the treatment and control groups was stable for repeated cross-sectional design (according to SUTVA).

According to literature, it can be noted that dietary supplement consumers are "younger" than medicine consumers. A comparative analysis of the age characteristics of dietary supplement consumers and drug users showed that the proportion of FS consumers aged 20–44 years in total is approximately 50%, approximately the same percentage of people aged 45–65 years consume medicines (Крылов and Череватая, 2006). No spillover effects were observed among either group.

The quantity of issued MAs for drugs and FS prior NPL shows a parallel trend. The graphical presentation of parallel trends is shown in the chart in Figure 4.13. below.

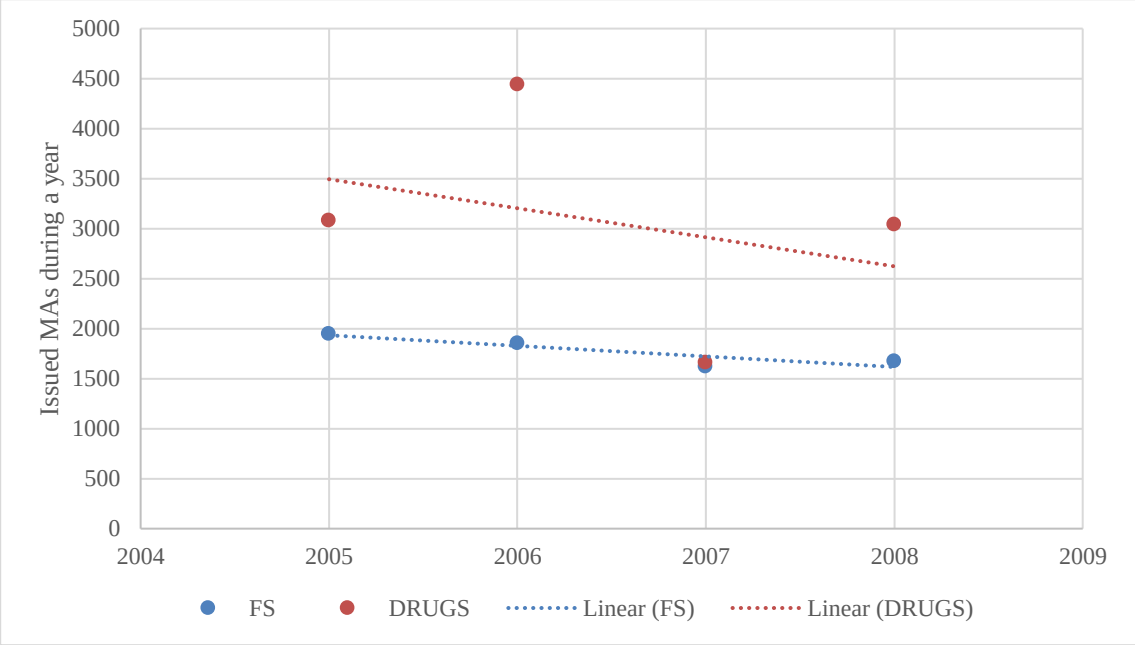


Figure 4.13. Quantity of issued Mas per year for medicines and food supplements prior to NPL

4.4.2. Regulatory performance evaluation for number of medicines vs. FS in 2008 and 2012

The calculation of the number of authorized medicines present in 2008 was performed based on the list of medicines that were registered, entered in the state register of medicines (SMR), and approved for medical use in the RF as of 15 December 2008 according to the electronic database of the state registry of medicines. A total of 37,555 entries were filtered, and unique registration numbers were left. For the final analysis, 20,836 entries were chosen.

The number of 5000 FS included in the state-register and allowed for import and circulation on the territory of the RF in 2008 was taken from the literature data (Туровская, 2010).

Further, the calculation of the amount of authorized medicines in 2012 was performed based on the State Register of Medicines as of 12 December 2012. A total of 20,209 entries were filtered, and only unique registration numbers were left. For the final analysis, 16,409 entries were chosen.

The amount of authorized medicines and FS (control) are shown in the tables below. The DiD calculation formula used is described in the Materials and Methods section.

Table 4.5.

Variables for DiD calculations and their numerical values

Coefficient	Calculation	Quantity
β_0	a	5000
β_1	c – a	15,836
β_2	b – a	4500
β_3	(d – b) – (c – a)	-8927

Table 4.6.

Number of FS(Control) and drugs included in SMR and DiD calculation

	FS(CONTR)	DRUGS
Year 1 (2008)	5000	20,836
Year 2 (2012)	9500	16,409
DIF	4500	-4427
DiD	-8927	

The difference in difference estimator shows a remarkable decrease in total number of medicines included in the SMR where the number of FS significantly increased. It can be seen, that before the NPL the number of drugs per SMR were 20,836 but FS 5000.

The yearly activities of FS registration significantly increased 5000 in 2008 and 9500 in 2012 respectively, showing a huge 90% increase.

The graphs as below show slopes of numbers of drugs vs. FS during two observational periods.

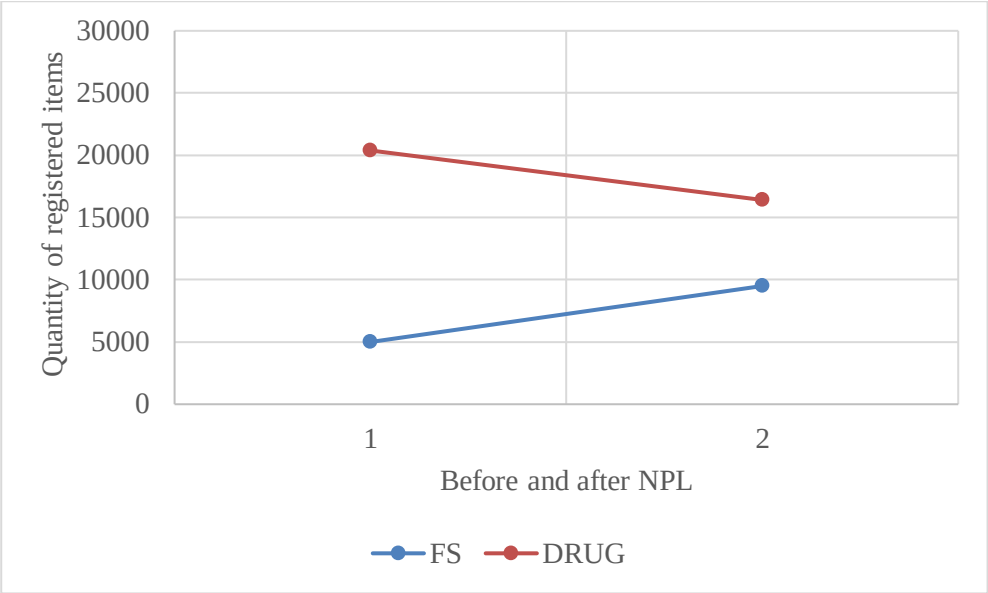


Figure 4.14. The graphical view of registered medicines per SMR and FS during two observational periods

On the X axis 1 stands for year 2008, 2 for 2012.

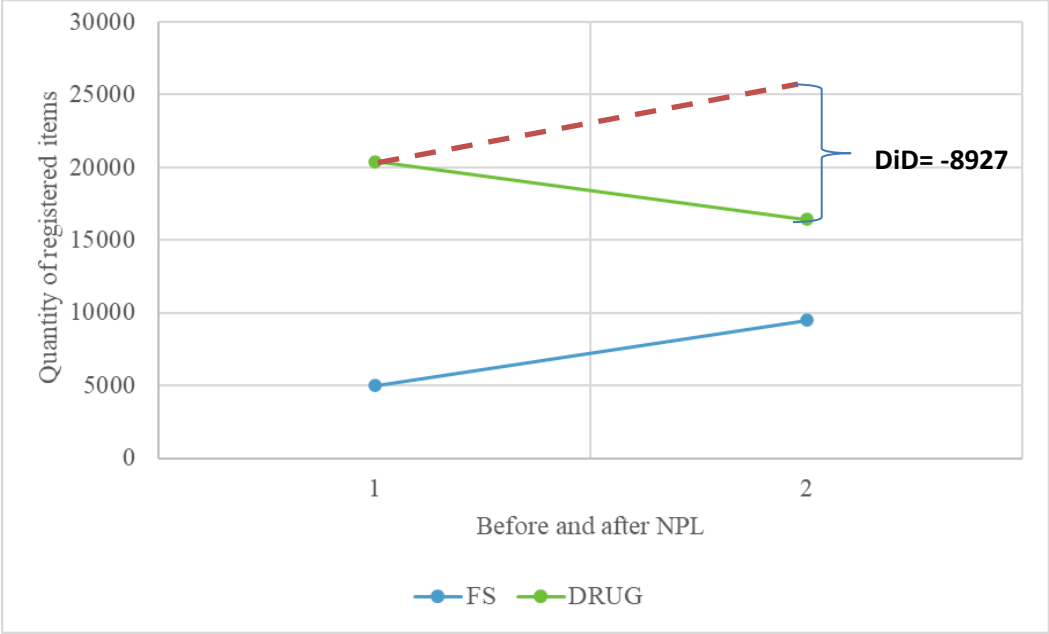


Figure 4.15. The graphical view of registered medicines per SMR and FS during two observational periods with DiD estimator

On the X axis 1 stands for year 2008, 2 for 2012. Dashed line shows DiD slope.

After NPL, there were 16,409 drugs in the SMR vs. 9500 in the FS. The difference was −4427 drugs and DiD, considering the FS trend of −8927. The fall reported was −21.25 %.

It is known that before a pharmaceutical product can be sold in a territory, it must be authorized with the national regulatory authority. However, due to the lack of clarity regarding procedures and technical and capacity constraints, the Russian regulatory system faced a negative impact due to the introduction of NPL. The key reasons for MA number fall are described in the previous chapters of the present research. It should be noted that during the period from 2004 to 2010, the inclusion of drugs in SMR was carried out by the head of the department responsible for the state registration of drugs, or by the person appointed by him (the executive officer) in the structure of the FGU. With the entry into force of the NPL and the Order of the Ministry of Health and Social Development of the RF No. 746n "On approval of the order maintaining the state register of medicines for medical use" of 21 September 2010 (Министерство здравоохранения и социального развития, 2010a), the maintenance and control of drugs was assigned to the Department of State Regulation of Drug Circulation and the Department of Informatization of the Ministry of Health and Social Development of Russia. The above mentioned and other normative acts such as Order N 1316-r (Прав. Рос. Федерации, 2010) significantly changed both the order and responsible executors of the SMR, its information structure, and functional role.

Thus, due to weak regulatory performance, we see a significant decrease in access to medicines for the population.

4.4.3. Regulatory performance evaluation for issued medicines MAs vs. FS in 2008 and 2012

The number of granted MAs per year was taken from statistics provided by FGU (Дранишникова, 2011) and the list of medicines registered in 2008 and 2012. The MAs of FS granted per year were taken from letters issued by the Chief State Sanitary Doctor of the RF (Главный государственный санитарный врач, 2009); (Главный государственный санитарный врач, 2007) and literature data (Резник, 2013).

The DiD calculation formula was used as per Materials and Methods section above.

Table 4.7.

Variables for DiD calculations and their numerical values

Coefficient	Calculation	Quantity
β_0	a	1675
β_1	c – a	1368
β_2	b – a	27
β_3	(d – b) – (c – a)	-1978

Table 4.8.

Number of MAs granted per year for FS(Control), drugs and DiD calculation

	FS(CONTR)	DRUGS
Year 1 (2008)	1675	3043
Year 2 (2012)	1702	1092
DIF	27	-1951
DiD	-1978	

The difference in difference estimator shows a significant decrease in issued MAs per year for medicines where the number of MAs for FS slightly increased. This came as a justification for the decreased productivity of the Authority after the implementation of NPL. We can see that before the NPL, the number of MAs issued for drugs were twice as much as FS, which after NPL introduction, was bound to fall to a much lower level. Before the NPL in 2008, drug MAs issued per year were 3043, whereas two years post intervention in 2012, the number was 1092. The difference was −1975 MAs/year and DiD assumed the FS trend to be 1978. The fall was obvious at −64.11%.

The yearly activities of FS registration remained stable at 1675 in 2008 and 1702 in 2012, accounting for a 1.61% increase.

The graphs below show slopes of issued MAs during two observational period

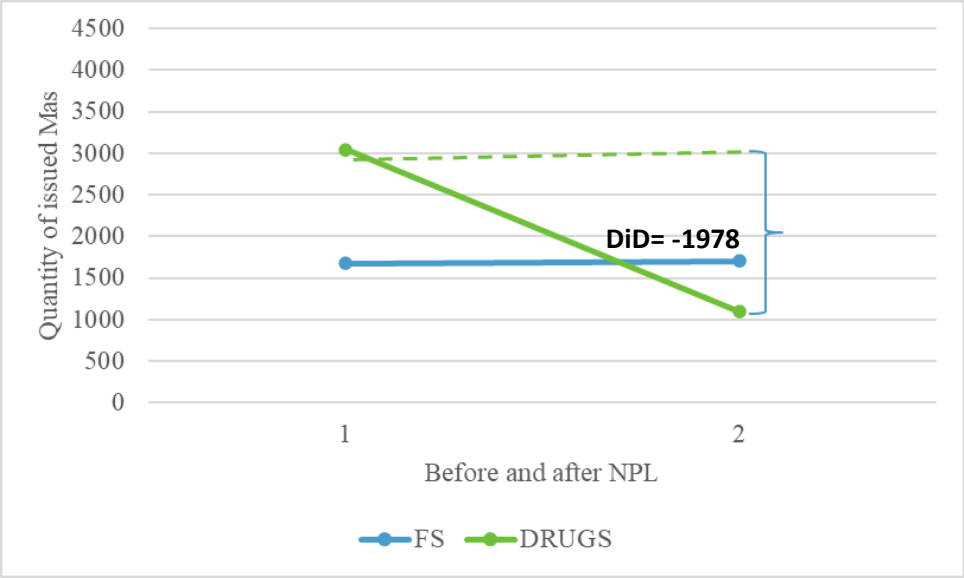


Figure 4.16. The graphical view of issued MAs/year during two observational periods

On the X axis 1 stands for year 2008, 2 for 2012.

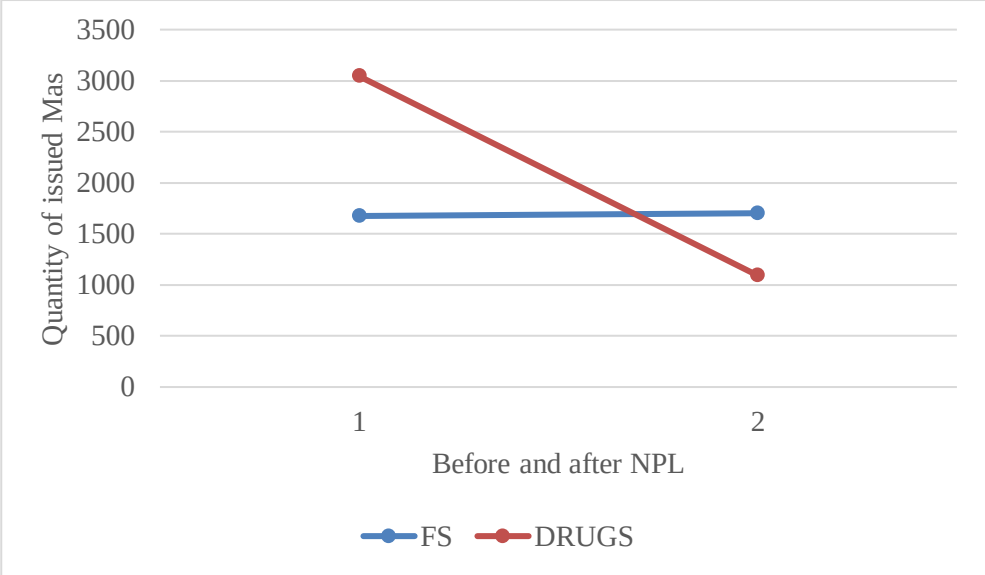


Figure 4.17. The graphical view of issued MAs/year during two observational periods with DiD estimator

On the X axis 1 stands for year 2008, 2 for 2012.

The above-mentioned regression calculations again emphasize the low productivity of the state authorities involved in the MA of medicines after the introduction of NPL, affecting

access to medicines. The NPL performance in terms of the authority's productivity can be considered insufficient.

The results of scientific research conducted at the Institute of Legislation and Comparative Law under the Government of the RF suggest that universal criteria for the accessibility of services in the social sphere counting medicines are physical, including geographical, accessibility, affordability, cultural accessibility, organizational accessibility (including informational), and social accessibility for certain groups of citizens (elderly, children, prisoners, and disabled people) (Цомартова, 2018). As we see from the calculations, the physical accessibility of pharmaceuticals decreased after the introduction of the NPL

4.4.4. Parallel trend assumption for drug safety reports in the RF vs. EU before NPL

The exchangeability, positivity, and SUTVA on one SAE unit reported in the EU were unaffected by the particular assignment of NPL treatment. Thus, the treatment was unrelated to an outcome at baseline, as EU and Russian PV systems do not interfere.

The available data show that the number of SAEs due to the active involvement of medical society and parties involved in drug circulation in the Russian pharmaceutical market increased from 0.008 reports per 1000 inhabitants in 2008 to 0.071 in 2010. Earlier data are not as significant as in 2008, and the active launch of regional drug safety monitoring began.

The EU PV reporting activities also continued to increase from 1.047/1000 inhabitants in 2008 to 1.229/1000 in 2010. The graphical presentation of parallel trends is shown in the chart below.

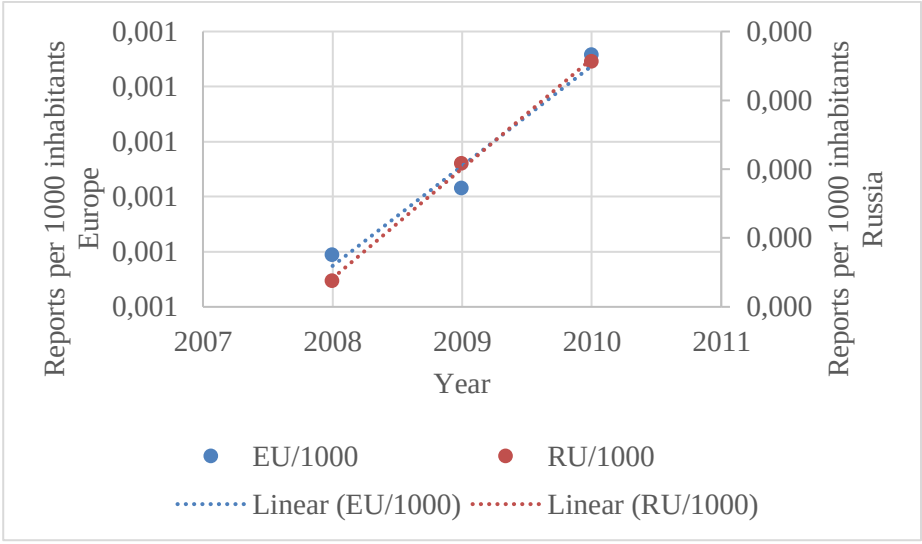


Figure 4.18. Quantity of SAEs reported in the EU and Russia prior to NPL

Treatment and control groups comparing the quantity of SAEs as seen from the trend lines in the chart above could be considered as being parallel in outcome prior to the treatment.

4.4.5. NPL performance evaluation based on drug safety reports in the RF vs. EU in 2009 and 2012

The NPL performance was assessed by calculating DiD based on the comparison of SAEs reported in Russia vs. European Union received by EMA.

The data of adverse drug reactions reported in Russia was taken from Roszdravnadzor reports (Росздравнадзор, 2011); (Росздравнадзор, 2013); (Росздравнадзор, 2014). The AEDs reported in the EU were extracted from European Medicines Agency reports (European Medicines Agency, 2009); European Medicines Agency, 2010; European Medicines Agency, 2011; European Medicines Agency, 2013a; European Medicines Agency, 2015). The number of inhabitants calculated was based on EU and Russian statistics data (Федеральная служба государственной статистики, 2019); (Eurostat, 2020). The times for statistical comparison were 2009 and 2012.

The reports used for calculations were individual case safety reports to the European Medicines Agency. Adverse drug reactions are reported to Roszdravnadzor.

Table 4.9.

Variables for DiD calculations and their numerical values

Coefficient	**Calculation**	**Quantity**
β_0	a	1,108
β_1	c – a	-1,066
β_2	b – a	1,302
β_3	(d – b) – (c – a)	-1,224

Table 4.10.

Number of SAEs received per year/1000 inhabitants in EU (Control), Russia and DiD calculation

	EU REPORTS/1000 Inhabitants (CONTR)	RUSSIA REPORTS/1000 Inhabitants
Year 1 (2009)	1,108	0,042
Year 2 (2012)	2,410	0,120
DIF	1,302	0,079
DID	-1,224	

The difference in difference estimator shows an increase in SAE reports per 1000 inhabitants in the RF as well as the EU. This came as a justification for the well-maintained Authority's productivity after the implementation of NPL. The FCMSM was established before and persisted by incorporating the same staff and was supervised by the same Roszdravnadzor after introduction of the NPL. Before the NPL in 2009, drug SAEs reported in Russia were 0.042, whereas two years post intervention in 2012, the number reported was already 0.120. The difference was 0.079 reports/year. However, DiD, assuming the EU trend, still showed a negative performance of −1.224 reports. Nevertheless, the increase in the reporting activity in Russia was 185.71%, whereas it was 117.51% in the EU.

The graphical presentation of the reporting productivity is shown in the Figure below.

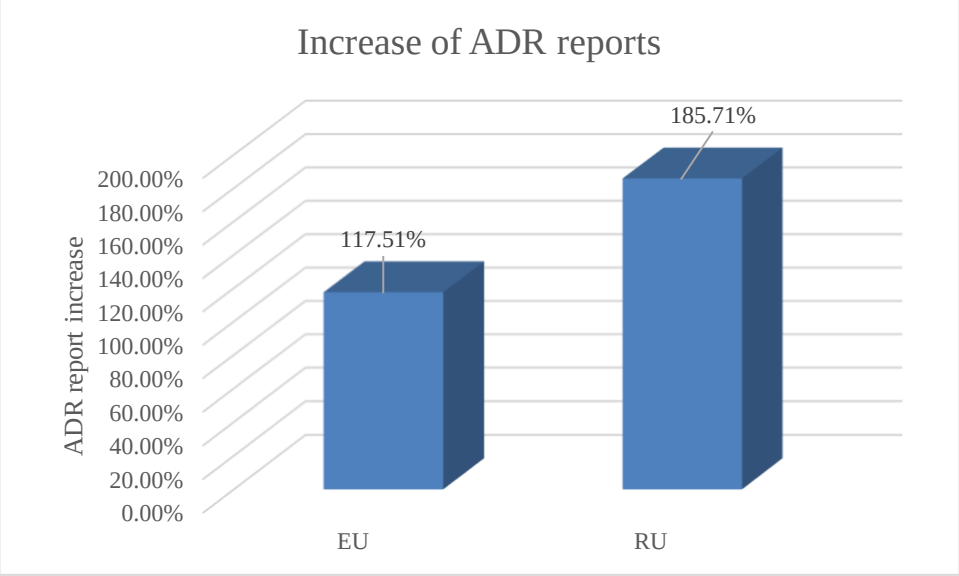


Figure 4.19. ADR reports increase in % from 2009 till 2012

The charts as in Figure 4.20. below show slopes of reporting activities during two observational periods.

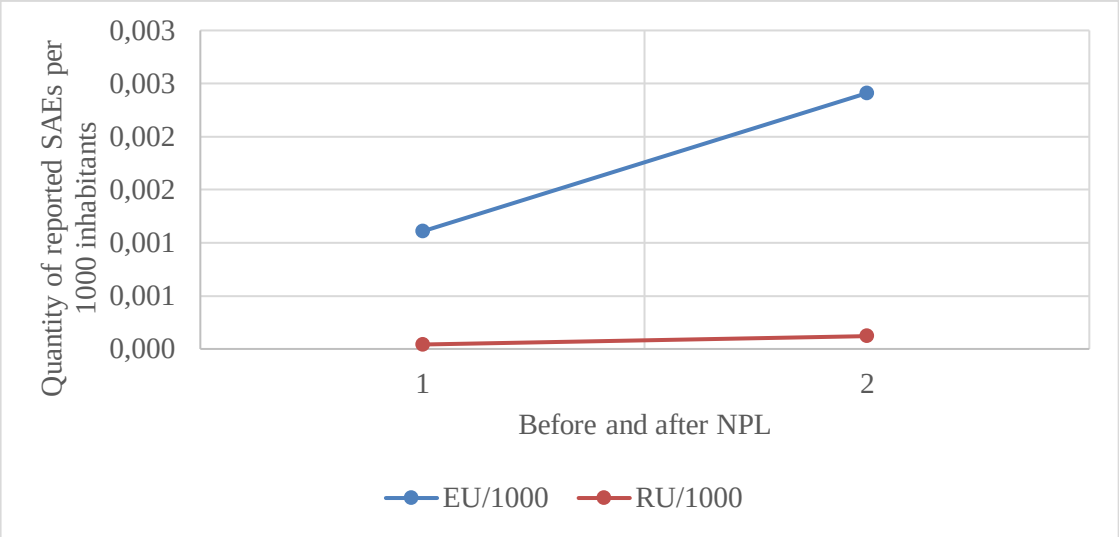


Figure 4.20. The graphical view of SAEs during two observational periods

On the X axis 1 stands for year 2009, 2 for 2012.

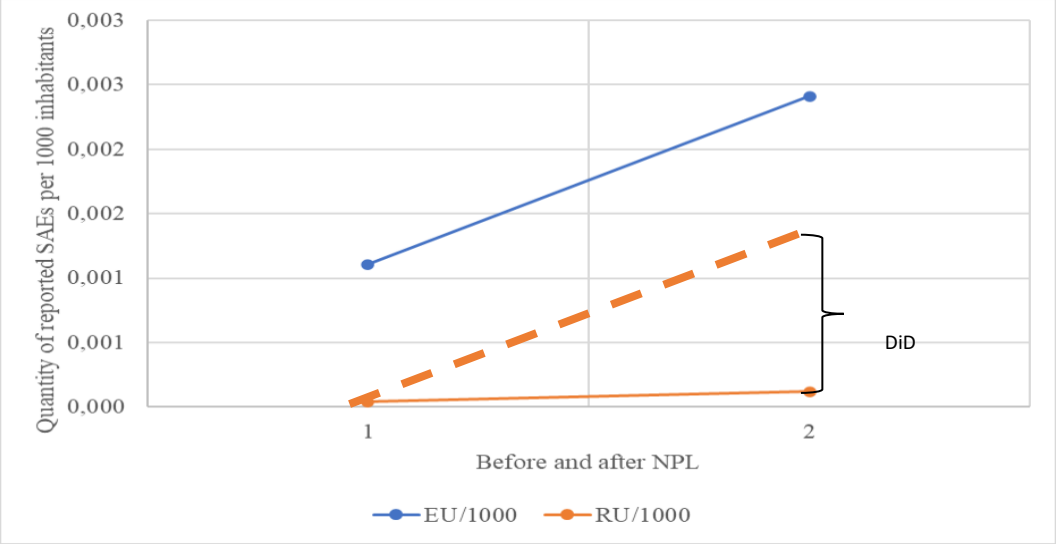


Figure 4.21. The graphical view of SAEs during two observational periods with DiD estimator

On the X axis 1 stands for year 2009, 2 for 2012.

The above-mentioned regression calculations emphasize a significant increase in societal activity and proper performance of the PV policy after NPL.

According to literature, despite the introduction of NPL, the most significant PV issue noted was the low activity of domestic manufacturers concerning the identification,

registration, and transfer of ADR information (Хосева and Морозова, 2013). However, the tendency of the PV system development in the RF is positive and follows international trends.

5. Discussion

At the beginning of the study, we noted that there was a keen interest in the pharmaceutical industry in processes around the introduction of NPL in 2010. However, only a limited number of articles covered the topic in detail, particularly in English.

This paper describes a unique authorization system created in the RF in 2010, for which there are no analogies in the world. Despite its novelty and declared benefits, the system continued to lack clear procedures and was unlike the best international experiences. The OL, since its introduction in 1998, was amended eight times until 2010. The NPL until July 2020 was amended 36 times.

The pharmaceutical regulatory administration performance would be less informative in terms of medicine access, as it requires an analysis of how well state officials have implemented particular regulations by counting the number of inspections or penalties imposed. The research method of the present study can provide meaningful feedback to officials, but it can only evaluate regulation performance from the point of view of governmental administrative resources. Research focused on administration performance is against ideal regulatory goals, not whether they work in terms of changing pharmaceutical activity outcomes.

Behavioural compliance evaluation is rarely used to refer to behavioural research. For example, the ban on non-prescription medicines sold in supermarkets might help in the evaluation of the number of wholesalers switching to internet-based purchases. As behavioural research refers to compliance assessments and defines the aim to determine the extent to which behaviour complies with certain regulation standards, it was not suitable for the present study. Lastly, the outcome performance fits well in the research presented in our study.

Whether the behaviour consists of drivers switching medicine wholesalers from supermarkets to the internet or governments implementing unanalysed decisions, behaviour matters only because of the resulting outcomes from those attitudes and evaluations. Therefore, they can be focused on outcomes such as defining the exact number of medicines registered under new legislation vs. former. At the same time, it is possible to measure the costs and benefits of the regulations adopted. Regardless of regulation implementation efficacy or compliance, the outcome performance serves as empirical research that focuses on outcomes. However, even in such types of studies, evaluations can be subsequently differentiated based on two core features of outcome evaluation, namely indicators and attribution. Based on literature (Coglianese, 2012), we referred to empirical measures of

outcomes such as outcomes of concern or other outcomes. The second feature taken into account in the present study, attribution, referred to the drawing of empirical inferences concerning the extent to which the legislation change has caused any indicator changes, allowing us to conclude whether a regulation is performing properly and enables us to attribute it causally to positive changes in indicators. As the basis of performance indicator choice, we also took into account that according to the literature, there are three different ways in which the term evaluation used must be distinguished: regulatory administration, behavioural compliance, outcome performance (Coglianese, 2012).

The selection of performance indicators was completed, considering the purpose of the present research to enhance the MA and SR process for pharma industry professionals and to find correlations between the MA process and access to medicines. Thus, to measure the performance of new Pharmaceutical Law we take into account that according to the latest literature Difference-in-Differences (DiD) is one of the most frequently used methods in impact evaluation studies. Based on a combination of before-after and treatment-control group comparisons, the method has an intuitive appeal and has been widely used in economics, public policy, health research, management and other fields. The DiD method is increasingly applied in regulatory certification and environmental policy (Fredriksson and Oliveira, 2019). The assumption of parallel trends implies that if untreated, the results for the NPL treatment and control groups are expected to change at the same rate. Thus, any difference in the differences in results between groups can be explained by policy, rather than by differentiated pre-existing trends in results (Ryan, 2009).

5.1. MA procedure before NPL

The registration procedure began with the signing of a contract and the submission of a number of documents to the Scientific Centre or NCOs. The Applicant or its authorized person must be the legal entity of the RF (*de facto*). The duration of registration, according to Law, took 210 days. The average time for MA was approximately 1.5 years. According to the field experience, the best-case scenario for generics was when the procedure took eight months.

Instruction for usage (the equivalent of Patient Leaflet in Europe) by a structure similar to the European SmPC was necessary. There was established so called “Typical clinical pharmacological file” (ТКФС), which was officially issued by the State Authorities (Минздрав, 2001), where all known data concerning special pharmaceutical preparations and combinations, their clinical usage, indications, side effects etc. were compiled. Instruction for

usage had to be in line with ТКФС and for generics according to the State Standard for pharmaceutical products.

Clinical testing is an essential stage of the drug registration procedure for NCE. The Federal Service on surveillance in healthcare and the social development of the RF (Roszdravnadzor) arranged to carry out control of clinical research quality, efficiency, and safety. Under the Federal Law on Medicines of 1998, drug developers and sponsoring companies were granted the right to choose clinical trial sites. No clinical trials were mandatory for generics; however, they might be assigned to a drug. The dossier had to be in Russian.

Roszdravnadzor issued an MA certificate with five years of validity. The dossier evaluation until 2010 was performed using FGU and 18 subcontracted NCOs. The dossier content was similar to the European Common Technical Documentation (CTD) (European Medicines Agency, 2004) except for an unique ND. In Table 1 of the Supplements of the present thesis, we compared dossier requirements with CTD. According to the table, a specific file Normative document contained a list of quality indicators of pharmaceuticals defined according to the results of the examination quality of the pharmaceutical, methods of its quality control as applied by the manufacturer. The ND consisted of the following documents:

- specification, where the quality parameters of a drug and evaluation of every parameter and limits are determined;
- description of composition (active ingredient and excipients) and appearance of the product;
- Description of identification, mean weight, pH, disintegration, dissolution, and content uniformity methods;
- microbiological quality, assay, and impurities methods;
- description of the container closure system, labelling, storage conditions, and shelf-life.

Thus, until 2010, the regulatory system in RF followed the international approach, except for the unique dossier format. International clinical trial data were accepted.

5.2. MA turmoil after NPL

The dossier evaluation process was completely renewed and administered by the new Ministry and subordinating institutions. The role of the FGU and subcontracted NCOs

diminished. New and inexperienced authority employees were involved in the MA process that made a “bottleneck” in the dossier evaluation flow.

The dossier content remained similar to that of CTD (European Medicines Agency, 2004), but the unique ND persisted. However, the dossier format to be submitted to the authorities was still not the CTD.

Interestingly, the same situation was observed in Sri Lanka, where the situation was compared to five chosen regulatory authorities from high-income countries and four regional ones. The authors concluded that optimizing pharmaceutical regulatory systems in low-income countries such as Sri Lanka in accordance with the system employed in high-income countries would help create an effective drug regulatory system based on decisions made by strict regulatory authorities. The results of their study prompted Sri Lanka to adopt the CTD format for regulatory filing of drug dossiers (Thambavita, Galappatthy and Jayakody, 2018).

In Table 2 of the Supplements of the present thesis, we compared dossier requirements with EU CTD (European Medicines Agency, 2004) and Russian in force after 2012.

The registration procedure had two stages: the first dossier evaluation for obtaining CT permission and the second quality control of medicines. There were just two CT exemptions. The first for drugs that are permitted for medical use in the RF for more than 20 years and for which study of bioequivalence is impossible. The second for drugs with respect to which international multicentre clinical trials were carried out, and some of them were held in the territory of the RF. Thus, irrespective of whether the medicine is NCE or generic, CT is mandatory. Thus, the CT requirement can be defined as another obstacle that decreases MA process productivity.

In recent research, some authors recommended expanding the list of drugs required for bioequivalence studies, and to use Biopharmaceutics Classification System-based biowaivers for some drugs at the time of generic registration, if scientifically justified. Moreover, some authorities in low-income countries have regulatory systems that rely on the review process already done by the International Council on Harmonisation (ICH) member countries or ICH observer countries. This process would be easier if a common dossier format is used during regulatory submission (Thambavita, Galappatthy and Jayakody, 2018).

The duration of registration, according to NPL for NCEs, was 210 days, whereas it was 60 days for generics. In reality, the evaluation time highly exceeded the defined timeframes. The key reasons for delay mentioned by local regulatory people were mandatory local clinical trials. The dossier had to be in Russian. The ministry issued an MA certificate with 5-year validity and unlimited after renewal.

Other authors referred to the same historical time stating that modern national regulatory practices in the drug market are based on the principles and approaches determined by the international policy in this area. In Russian industry documents, one can find references to harmonisation with international standards and regulations. However, the NPL practice and the proposed amendments represent a combination of elements borrowed from foreign experience and proprietary proposals that do not always have analogues in global practice. Given this, it seems timely to refer to the European Union's experience, which has achieved some success in regulating the circulation of drugs (Мешковский, 2014).

During the turmoil period caused by NPL, the local pharmaceutical industry endured serious challenges. Because of a high level of self-organization, excellent issue-solving skills, and the perseverance of the people, a significant negative impact of these regulatory affairs system changes was prevented. However, before the present study, the impact thought to have been overcome by the aforementioned efforts was not justified by controlled statistical calculations. Our current research shows the weak performance of NPL and a decrease in the number of medicines registered. By our opinion, the aforementioned personal skills of local regulatory staff made the health impact of the medicine shortage less visible in the State perspective. Moreover, this was a good example of how citizens can influence governmental decision makers for the improvement of the legislation and institutional performance.

The impact of the activity on the general public and pharmaceutical industry representatives led to a process in which the latest legislation changes were implemented at several sites. This process included the Analytical Centre of the Russian Government, representatives of patient and medical communities, businesses, and the 20 largest professional associations.

As observed, the latest amendments had not been adopted through hasty decisions, and the interaction between the government and pharmaceutical industry associations became more efficient and thoughtful.

In health systems, access to medicines depends on five main factors: availability, affordability, accessibility, acceptability, and quality (Tiguman, Silva and Galvão, 2020). In our study, we found that due to the regulatory burden after the introduction of NPL, availability and accessibility of medicines in RF was impacted. Our findings correspond to the statement that national regulatory authorities are the key government institutions that promote access to quality-assured medicines and combat falsified medical products, however despite progress, regulatory capacity in low-income countries is still insufficient (Roth *et al.*, 2018).

A recent qualitative, cross-country study carried out in four Latin American countries concluded that the judicialization of access to medicines emerged regardless of constitutional

protection or health system population coverage. Among the causes, was the difficulty faced in guaranteeing access to covered medicines. Their results suggested that applying the adopted theoretical model creates the possibility of identifying critical points to guide policymakers to improve the performance of health systems and to control lawsuits for access to medicines (Vargas-Pelaez *et al.*, 2019).

Overcoming the burden caused by NPL, MA systems have slightly recovered, and in March 2019, there were 20,192 entries in the authorized medicines list vs. 20,836 entries in 2008. As mentioned earlier, regarding NPL, until 2020, it has been amended 36 times, and neither CTD format nor national CT issues are solved.

Thus, we hope that the present study will be helpful for the pharma industry and policy makers to improve their performance in a changing environment.

5.3. The EAEU MA legislative framework

To be in accordance with international regulatory approaches, which were definitely beneficial for companies in the domestic pharmaceutical industry that want to be successful exporters, a harmonized position of the legislation was considered. To address such issues in the future, common Eurasian Economic Union legislation was introduced.

As stated in the MCA, the decisions of the EUEC governing circulation of pharmaceuticals are prepared from international norms (Lozda, 2017b). Such legal provisions assume that the most likely functioning of the common market even with these norms would face the same arbitrary interpretation of regulatory issues by state officers so often met with in the Commonwealth of Independent States. Thus, a draft set of rules for the registration and examination of medical products define the following pathways for pharmaceutical registration in the EAEU:

a) a mutual recognition procedure implemented by any of the national competent bodies;
b) a decentralized procedure implemented by any of the national competent bodies;
c) and the national procedure executed by each national competent authority (Lozda, 2017b).

The dossiers of pharmaceuticals already registered in MS and submitted prior to the empowerment of MCA must be compliant with the requirements of the EAEU until December 31, 2025 (Lozda, 2017b).

The applicant registering the pharmaceutical can choose for the registration to either be carried out following the EUEC rules or under the legislation of the MS until December

31, 2020. The drugs that MS registers under national laws shall be admitted to trading only in the territory of that State (Lozda, 2017b).

Medicinal products registered under the national laws of the MS should be brought into line with the requirements of the MCA by December 31, 2025.

The Marketing Authorization dossier must be provided as a CTD. All registration documents must be submitted in Russian or with a Russian translation. The documents of Modules 3, 4, and 5 may be provided in English with mandatory translation into Russian of the following sections:

1) Module 3: specification (3.2.P.5.1.),
2) Analytical methods (3.2.R.5.2.),
3) Validation of specifications (3.2.R.5.6.).

A risk management plan may be provided in English with a mandatory translation of the resume into Russian (Lozda, 2017b).

Despite a detailed description of regulatory pathways, potential applicants will be obliged to follow specific national requirements as usual.

For example, all documents marked as to be "Certified in the prescribed manner" are assumed to be notarized or apostilled with notarized translation. Among such documents, a Power of Attorney issued by Applicant to the Person acting on their behalf, Certificate of Pharmaceutical Product, or a GMP (European Commission, 2011) certificate could be mentioned. Another specific issue is that any original document issued by the applicant must contain not only original signatures but also a company stamp. This is quite a strange requirement for Western companies, as most authenticity of documents is confirmed by the original signatures of responsible persons.

Additionally, a superficial reading of Project of Rules for registration and examination of medical products gives the impression that a nationally important document ND is no longer needed due to the CTD format. However, the ND is still required and must be included in part 3.2.P.5.2. of CTD Module 3. Moreover, all the quality and analytical standards will be based on the Pharmacopeia of Union, which assumes the harmonisation of pharmacopoeias of five MS. Colleagues who are already involved in ND preparation can likely imagine potential issues with harmonising these methods, for example, the possible difficulty of harmonising methods of the United States Pharmacopeia or European Pharmacopoeia with Russian Pharmacopeia (Lozda, 2017b).

At a meeting of the Board of the EEC held on January 17, 2017, the members of the Eurasian Economic Union Pharmacopoeia Committee (EEUPC) were approved. Among the tasks of the EEUPC is to approve the monographs of the first volume of the Pharmacopoeia of

the Eurasian Economic Union. At present, there are approximately 180 monographs prepared but not yet approved.

Thus, at the end of 2017 despite enormous workload with an intention to easy market entrance and overall unification, all the efforts led to nowhere and the Russian MA system proceeded to function autonomously (Lozda, 2017b). Though, there were several reasons for the common pharmaceutical legislation implementation delay. Russia's late ratification of the MCA, adopted on December 23, 2014 could be mentioned as the first.

Second, to ensure the policy could work, the EUEC prepared a package of 25 supranational regulations. The Council of the EUEC discussed the most "sensitive" issues of the package (19 of 25) and because of disagreements on the central document, Rules for Registration and Examination of Medical Products, decided to postpone the signing of the papers. The key issue was that Russia insisted on including the procedures to establish interchangeability of medicines during their registration process.

Interchangeability was one of the most important issues in Russia because of the possibility of substituting one drug for another within the state reimbursement system and other governmental procurements. Once interchangeability is addressed, the most significant impacts on drug supply are population, pharma competition, and pricing. Thus, after EAEU member states resolve all mentioned disputes, a whole EAEU document package was expected to be signed.

Finally, at a meeting of the EUIC, the heads of MS governments approved the above-mentioned package on August 12, 2016. It was also noted that there is now a major agreement on how the common policy will start. Representatives of MSs decided that a free movement of medicines within EAEU territory will first be initiated. Then, the questions related to public procurement will be addressed now that MSs have come to an understanding of how they will adjust common legislation regarding medicines interchangeability.

Another crucial reason for the common policy delay was the absence of the EAEU pharmacopoeia. In summary, there were almost no legal obstacles to implementing common EAEU pharmaceutical legislation to start a common market. Core document packages were ready for approval by the Council of Eurasian Economic Commission. Although these legal documents referred to international norms, and some of them, such as the document regarding good practices, even referred to the requirements of the European Union and Organization for Economic Co-operation and Development, although we did not exclude some local peculiarities. Possible issues could be caused even by something as slight as misinterpretation during the translation of records. The author himself participated in several court cases related to consequences caused by legally incorrect interpretations of the EU acts into the national

languages of member states. Thus, regarding challenges, establishing the common EAEU pharmaceutical policy is not going to be easier than existing national procedures or those of the EU, and regular follow-up is needed.

From our perspective and considering the present study, we see the following challenges during the MA process within the EAEU. Dossier preparation itself requires documents that are certified in the prescribed manner, the presence of ND, correctly translated parts, etc. The approval of GMP compliance to the requirements of the EAEU requires site inspection by MS authorities. Clinical trials must be performed in the territory of the EAEU. Finally, the package leaflet user test, which is part of Dossier Module 1, must be performed in the EAEU Reference State if applicable. The regulatory bodies of the EAEU have expressed the will to show a harmonised opinion on excessive repeated clinical trials. In addition, there has been significant progress in the introduction of the CTD format, harmonised requirements for the registration dossier, and the examination approach for original and generic drugs.

Therefore, if the key obstacles decreasing NPL performance are not considered, the common EAEU policy could affect the access to medicines in a larger territory.
Unfortunately, even in 2020, the common EAEU MA system has not started yet. Therefore, Latvian and EU manufacturers' expectations for easy entrance into the common pharmaceutical market of the EAEU are still in the project phase.

5.4. PV system in the RF

Despite substantial breakthroughs regarding local requirement unification with the best world practices, there were still several tasks to complete in Russia. Among these tasks were the generation of a harmonised list of “birth dates” and the timing of PSUR filing. The introduction of the dictionary of MedDRA medical terminology (Dutta, 2020) into the Russian language was not available. Additionally, PV system inspections were going to be a serious issue for both authorities and market operators.

As seen from the present research, drug safety reporting improved after the introduction of NPL.

Overall, national legislation in Russia has been unified according to the requirements of the EUGVP. However, some issues remain. Thus, in Russia, local adverse event reporting forms are not consolidated with ICH E2B (European Medicines Agency, 2013b) as defined in the EUGVP. There are also differences regarding express reporting and PSUR submission timelines, as described in the table below.

Table 5.1.

Reporting and PSUR timelines among EAEU countries

Item	EAEU	Russia
Individual case reporting within 15 days	a) serious AD occurred in MS, b) serious unexpected AD from other states	a) serious AD occurred in locally, b) serious unexpected AD from other states
Express reporting	none	serious AD with a fatal or life-threatening outcome within 3 days
PSUR submission schedule	once every 6 months for 2 years from the international registration	once every 6 months for 2 years from the international registration
	annually over the next 2 years	annually over the next 2 years
	further – every 3 years	further – every 3 years

Since 2008, significant changes have been introduced into the national PV system, and the most obvious beneficial effect was achieved after empowering NPL.

The latter corresponds to the conclusions made by other authors. They also observed that there were also differences regarding express reporting and PSUR submission timelines. The RF pharmaceutical market needs active improvement of drug safety surveillance tools since this system takes into account the social and economic aspects of the development of all states without exception. The social significance of the drug safety problem contributed to the consolidation of most countries' efforts and the formation of a unified PH system under the auspices of the EAEU. Further improvement of PV in Russia and the EAEU will provide a healthcare system with high-quality and safe drugs (Gildeeva and Belostotsky, 2019).

The findings of our research correspond to the opinion that the evolution of PV cannot occur in isolation, and it must be part of a larger effort to improve global clinical research and development and reform the regulatory systems (Furlan *et al.*, 2016). It is noted that international organizations such as Alliance for Clinical Research Excellence and Safety would bring together an alliance of stakeholders who share the belief that a high-performing global system that provides the society with access to safe, effective, dependable, and affordable medicines is an essential societal good that benefits all stakeholders (Koski, Tobin and Whalen, 2014).

According to the latest data, the reported number of SE in the RF in 2019 was 28619, that is 0.195 per 1000 inhabitant, whereas in the EU it was 0.358 (Росздравнадзор, 2020); (European Medicines Agency, 2020). Thus, the way the RF conducts PV activities corresponds to the best international practices; avoiding national peculiarities would lead to further success.

6. Conclusions

1. Despite the intention of synchronizing the MA system with the best international practices, the RF still has its own peculiarities for which there are no analogies.

2. The performance of the NPL and consequential administrative reforms during the observational periods 2008 and 2012 in terms of the number of registered medicines and issued MAs per year was lower than in the control legislation regulating FS, which led to decreased access to medicines during the observational period.

3. The performance of the NPL during the observational periods 2009 and 2012 in terms of PV reporting activity was lower than that in the EU; however, it maintained a stable positive trend following the best international practices and maintaining the historical state authorities involved in the PV process.

7. Practical recommendations

From the present research, a few recommendations can be made.

1. The country-specific. drug regulatory requirements on which international society has common agreement, such as clinical trial data acceptance, must be clearly introduced procedurally prior to the implementation of legislative changes.

2. Society's opinion must be considered prior to the implementation of the legislation, as the apparent reason for overcoming regulatory turmoil after the NPL was the high level self-organization among the local regulatory specialists.

3. Various professional associations were involved in the NPL project discussions, but only a few of their suggestions were considered. A more detailed evaluation of a professional's opinion has to be considered by stakeholders.

4. Consultations with the society of pharmaceutical professionals on regulatory legislations are crucial as they account for field experience and ensure the consideration of recommendations of the impacted party.

5. The public consultations for legislative projects must not be formal, as they will lead to consequences such as more difficult regulatory alterations during implementation.

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Approbation of the study – publications and thesis

Doctoral thesis is based on following SCI publications:

1. Lozda, R. Regulatory Issues of Voluntary Certification of Food Supplements in Russia. Ther Innov Regul Sci. 2019, Jan 24. doi: 10.1177/2168479018822795. [Epub ahead of print] PubMed PMID: 30678464.

2. Lozda, R. Pharmacovigilance Requirements in Russia and Kazakhstan. Pharmind, Nr. 12, Seite 1681 (2017) See more at: http://www.ecv.de/beitrag/pharmind/Pharmacovigilance_Requirements_in_Russia_and_Kazakhstan

3. Lozda, R. The Common Pharmaceutical Market of the Eurasian Economic Union. A Regulatory Review. Therapeutic Innovation & Regulatory Science, vol. 51, 6: pp. 751–755, May 11, 2017. See more at: http://journals.sagepub.com/doi/full/10.1177/2168479017701978

4. Lozda, R. Regulatory System Changes in Russia: A Historical Review and Future Perspectives. *Therapeutic Innovation & Regulatory Science*, February 7, 2016 doi: 10.1177/2168479015627853. See more at: http://journals.sagepub.com/doi/full/10.1177/2168479015627853

Results are reported in following conferences

International conferences:

Lozda, R. Sharing experiences of registration under the new Russia Law on Drugs 3rd Scientific Conference. Regulatory Affairs in Russia, the CIS and Turkey. 14th – 16th November 2012. By Informa Lifesciences. http://www.mkvt.hu/PDF/ra_in%20_russia.pdf

International seminars:

Organized by the FORUM Institut für Management an international group of institutes that concerns itself with the training of corporate specialists and executives.

Lozda, R. The Eurasian Economic Union (EAEU) – Changes in Regulatory Affairs, PV & Distribution. 28 January 2016 in Frankfurt.

Lozda, R. Marketing Authorisation in the CIS Countries/Russia. Russia, Belarus, Ukraine and Kazakhstan in focus. 20–21 August in Berlin.

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Supplements

Table 1.

Content of dossier RU system vs. CTD before 2010

Documents	RU File	CTD
Letter of intention Application, name of the pharmaceutical preparation, List of active ingredients Description of the drug and its packaging, shelf life and storage conditions		1.0 Cover Letter 1.2 Application Form
Dosage, instruction for use		1.3.1 SPC, Labelling and Package Leaflet
Power of Attorney issued by the manufacturer to the authorized company for carrying out registration procedure (notarized original with apostil)	F 1	1.2 Application Form (Annex 6.4)
A copy of the Free Sales Certificate (must be notarized and apostilled)	F 1	
Certificate of pharmaceutical product (must be notarized and apostilled)	F 1	
A copy of the license of pharmaceutical manufacture (must be notarized and apostilled)	F 1	1.2 Application Form (Annex 6.6)
A copy of the GMP certificate (must be notarized and apostilled)	F1	1.2 Application Form (Annex 6.9) * Does not require EU approval (eg. FDA)
A copy of the Certificate of manufacturer registration in their own country (must be notarized and apostilled)	F 1	1.2 Application Form (Annex 6.3)
The original Certificate of analysis of the drug and its active substance (must be signed and stamped by manufacturer)	F 1	Mod. 3.2.S.4.4; 3.2. P.5.4
A copy of the Certificate of trademark (must be signed and stamped by the manufacturer)	F 1	
Information of registration of the drug in the country of manufacture and other countries	F 1	1.2 Application Form (Annex 6.15)

Table 1. Continued

Colour mock-ups of the primary and secondary package with labelling text in Russian	F 1	1.2 Application Form (Annex 6.17)
Report of the pharmacological (specific) activity study substantiating the indications for use which are formed and described in the instruction	F 2	Mod 2.7 Mod 4 Mod 5.3.5.1
Test report of the drug toxicity (acute, sub acute, sub chronic, chronic toxicity)	F 2	Mod 2.6 Mod 4
Test report of the specific influences (cancerogenity, mutagenic and teratogenic effects, embryo-toxicity, allergic and local-irritative effects)	F 2	Mod 2.4; 2.6 Mod 4
Clinical trial results	F 2	Mod 5
Copies of publications of the medicine usage in clinics after its registration in the country of origin	F 2	Mod 5.3.6
Report of pharmacokinetics of the pharmaceutical study and its bioequivalence to the original drug (generics)	F 2	Mod 3.2.P Mod 5.3.1.2
PSUR data (5 years)	F 2	Mod 2.5
The summary of method of the drug manufacturing (must be signed and stamped by manufacturer)	F 3	Mod.2.3
ND. The complete description of the quantitative and qualitative control methods with references to the pharmacopeia and specification (must be signed and stamped by manufacturer)	F 3	Mod 3
Stability data of three drug series – by date	F 3	Mod 3.2. P.8.3
Patterns of the spectrums and chromatograms of the drug	F 3	Mod 3

F – stands for folder, Mod – module.

Table 2.

Content of dossier RU system vs. CTD after 2012

RU dossier	CTD
Letter of intention Application, name of the pharmaceutical preparation, List of active ingredients Description of the drug and its packaging, shelf life and storage conditions	1.0 Cover Letter 1.2 Application Form
Dosage, instruction for use	1.3.1 SPC, Labelling and Package Leaflet
Power of Attorney issued by the manufacturer to the authorized company for carrying out registration procedure (notarized original with apostil)	1.2 Application Form (Annex 6.4)
A copy of the Free Sales Certificate (must be notarized and apostilled)	
Certificate of pharmaceutical product (must be notarized and apostilled)	
A copy of the license of pharmaceutical manufacture (must be notarized and apostilled)	1.2 Application Form (Annex 6.6)
A copy of the GMP certificate (must be notarized and apostilled)	1.2 Application Form (Annex 6.9) * Does not require EU approval (eg. FDI)
A copy of the Certificate of manufacturer registration in their own country (must be notarized and apostilled)	1.2 Application Form (Annex 6.3)
The original Certificate of analysis of the drug and its active substance (must be signed and stamped by manufacturer)	Mod. 3.2.S.4.4; 3.2. P.5.4
A copy of the Certificate of trademark (must be signed and stamped by the manufacturer)	
Information of registration of the drug in the country of manufacture and other countries	1.2 Application Form (Annex 6.15)
Colour mock-ups of the primary and secondary package with labelling text in Russian	1.2 Application Form (Annex 6.17)

Table 2. Continued

Report of the pharmacological (specific) activity study substantiating the indications for use which are formed and described in the instruction	Mod 2.7 Mod 4 Mod 5.3.5.1
Test report of the drug toxicity (acute, sub acute, sub chronic, chronic toxicity)	Mod 2.6 Mod 4
Test report of the specific influences (cancerogenity, mutagenic and teratogenic effects, embryo-toxicity, allergic and local-irritative effects)	Mod 2.4; 2.6 Mod 4
Clinical trial results	Mod 5
Copies of publications of the medicine usage in clinics after its registration in the country of origin	Mod 5.3.6
Report of pharmacokinetics of the pharmaceutical study and its bioequivalence to the original drug (generics)	Mod 3.2.P Mod 5.3.1.2
PSUR data (5 years)	Mod 2.5
ND. The summary of method of the drug manufacturing (must be signed and stamped by manufacturer)	Mod 2.3
The complete description of the quantitative and qualitative control methods with references to the pharmacopeia and specification (must be signed and stamped by manufacturer)	Mod 3
Stability data of three drug series – by date	Mod 3.2. P.8.3
Patterns of the spectrums and chromatograms of the drug	Mod 3

Table 3.

EUGVP terms

Adverse reaction – an untoward reaction of the body associated with the use of a drug (or investigational) and assuming the existence, at least, of a possible relationship with the use of a suspected drug.
Unexpected adverse reaction – untoward reaction, the nature, severity or outcome of which does not correspond to the information contained in the current summary of medicinal product characteristic.
Serious adverse reaction – an undesirable reaction that leads to death, threatens life, requires hospitalization or its prolongation, leads to persistent or severe disability or disability, to congenital anomalies or malformations, calls for medical intervention to prevent the development of these conditions. Expedited reporting requirements for MAH are as follows:
a) on serious adverse reactions found on the territory of MS;
b) on serious adverse reactions found on the territory of MS;
c) on serious unexpected adverse reactions found in the territories of other states.
In addition to above mentioned case reports, any safety information from other observations that could change the risk-benefit evaluation for the medicine such as:
a) excess of the expected frequency of serious adverse reactions;
b) restrictions on the distribution of the medicinal product and withdrawal of the drug from the market;
c) rejection of renewal, cancellation or suspension of the validity of marketing authorizations in the other countries due to the safety reasons;
d) significant changes to the recommendations on medical use in the other countries due to the safety reasons;
e) safety issues identified during the non-interactive post-approval studies, clinical research or preclinical research;
f) safety data established during a signal evaluation and can influence the "benefit-risk" ratio;
g) safety issues associated with the off-label use and erroneous information in patient leaflet or labelling;
h) inadequate efficacy of drugs used in pathology that poses a life-threatening situation, as well as vaccines and contraceptives;
e) safety issues of the raw and (or) their supply.