Original Article

Circulation of Immunobiologicals in the Russian market

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ABSTRACT

This study aimed at defining the peculiarities of immunobiologicals' circulation in the Russian pharmaceutical market. In the system analysis of the regulatory framework for the national regulation of medicine circulation for 2014–2019, it has been revealed that the requirements set to immunobiologicals were stricter. The comprehensive combination of the pharmaceutical and sanitary-epidemiological regulation for all circulation subjects has been an important feature. Since the end of 2019, manufacturers and holders of registration certificates must comply with a new procedure for introducing vaccines, toxoids, toxins, serums, immunoglobulins, and allergens into circulation. The Russian market of the basic groups of immunobiologicals has largely depended on the development of the domestic pharmaceutical industry, regulated by the Ministry of Industry and Trade of Russia.

Keywords: Immunobiologicals, immunoprophylaxis, national requirements for storage and transportation, new rules for entry into circulation

Introduction

Generally, the increasing growth in science and technology has generated many changes in terms of health services, which has resulted in the demand for retraining to maintain competencies and job skills.[1] The immune system is known to be very sensitive to changes in the body and general health.[2] The circulation of immunobiologicals in Russia has important features characterized by expanded requirements for all market participants. The statutory regulation on the circulation of immunobiologicals was changed in 2017 and continues changing today. The key changes in the entry of medicines of this group into circulation would come into force at the end of 2019.

Methods

The content analysis of the national legislative and statutory regulation on the circulation of immunobiologicals has been carried out. Based on the hierarchy of the national system of legal regulation of "federal law – bylaws", the study of the substantive components of the current regulatory documents covering such keywords as immunobiologicals, immunoprophylaxis (Consultant and Garant legal bases), included: system analysis of the requirements for the subjects of the pharmaceutical market and the identification of features for individual stages of circulation determined by various regulators (Ministry of Health of Russia, documents of the sanitary-epidemiological regulation), comparative and actualization analysis based on the changes that have been made to the current regulatory documents for 2018 (State Pharmacopoeia XIV edition, Federal Law No. 449-FZ), as well as identification of the prospects for the development of the market of immunobiologicals for the period up to 2030 (Draft Strategy for the Development of the Pharmaceutical Industry until 2030, publications on the development of the Russian pharmaceutical market and the general market of medicines of the Eurasian Economic Union).

Results

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In accordance with Federal Law No. 61-FZ dated 12.04.2010 on "Circulation of Medicines", as well as a new general pharmacopoeia article of Pharmacopoeia XIV edition GPA.1.7.1.0018.18 (instead of GPA.1.8.1.0002.15), immunobiologicals have been medications intended to form active or passive immunity, diagnose the immunity, or diagnose specific acquired changes in the immunological responses to allergenic substances.[3-5] Immunobiologicals include six groups of medications: vaccines, toxoids, toxins, serums, immunoglobulins, and allergens. Federal Law No. 157-FZ dated 17.09.1998 on "Immunoprophylaxis of Infectious Diseases" has identified immunobiologicals for the immunoprophylaxis (vaccines, toxoids, immunoglobulins, and other medical products) intended to create specific immunity to infectious diseases. Order of the Ministry of Health of Russia No. 749 dated October 31, 2018, approved general pharmacopeia articles and pharmacopoeial articles, and also specified that they constituted the new State Pharmacopoeia XIV edition.

As a result of the content analysis of the State Pharmacopoeia XIV edition, it was revealed that by January 1, 2022, the regulatory documentation for the registered medicines and their pharmaceutical substances, as well as pharmaceutical substances produced for sale and included in the state register of medicines for medical use would have to be brought into compliance with the approved general pharmacopeia articles and pharmacopeia articles.

General pharmacopeia articles for immunobiologicals in the State Pharmacopoeia XIV edition have been the followings:

Immunobiologicals GPA.1.7.1.0018.18 instead of GPA.1.8.1.0002.15;

Vaccines and toxoids GPA.7.7.1.0004.15;

Allergens GPA.1.7.1.0001.15; and

DNA vaccines GPA.1.7.1.0013.18 introduced for the first time.

Pharmacopoeia articles for immunobiologicals have the following serial numbers in Pharmacopoeia XIV edition:

Allergens: 547, 569, 613, 614;

Anatoxins: 548 – 555;

Vaccines: 556 – 568, 570 – 583, 595 – 602;

Immunoglobulins: 584 – 592; and

Serum: 587 – 592.

It is necessary to pay attention that this has been the first time when Pharmacopoeia XIV edition introduced pharmacopeia articles for the following immunobiologicals:

- Vaccine (adsorbed) against pertussis, diphtheria, tetanus and hepatitis B, suspension for intramuscular injection of FS.3.3.1.0049.18 introduced for the first time;
- A combined vaccine against hepatitis B and diphtheria-tetanus toxoid with a reduced content of antigens adsorbed, suspension for intramuscular injection FS.3.3.1.0050.18 introduced for the first time;
- Hemophilic, type b, conjugated, and lyophilisate vaccine for preparation of a solution for intramuscular injection FS.3.3.1.0055.18.
- Immunoglobulins: anti-tetanus human immunoglobulin FS.3.3.2.0010.18.

State regulation pays special attention to the stages of storage and transportation of immunobiologicals.

Transportation and storage of immunobiologicals are determined by several affiliated regulatory documents:[6]

- General pharmacopeia article GPA.1.1.0010.18 on "Storage of medicines".
- General pharmacopeia article GPA.1.7.1.0018.18 on "Immunobiologicals".
- Pharmacopoeia articles in Pharmacopoeia XIV edition.
- Regulatory documentation of manufacturers.
- Resolution of the Chief State Sanitary Doctor of Russia No. 19 dated 17.02.2016 on Approving Sanitary-Epidemiological Regulations SP 3.3.2.3332-16, "Terms and Conditions for Transportation and Storage of Immunobiologicals" (hereinafter referred to as the Regulations).

Recently, more convenient and recent technologies have found new methods that not only have provided better storage conditions and optimum storage temperature as per the requirement of the storage conditions but, when compared to the traditional methods, they have been much more convenient.[7] The storage conditions should ensure the safety of all properties of the medicine during the appropriate period of its shelf life. As a rule, the storage temperature must be within 2 – 8 ℃, unless otherwise indicated in the pharmacopeia monograph. In all cases, specialists should be guided by the instructions for use.

As a rule, temperature and other transportation requirements should not differ from those for storage. The possibility of transporting the medicine at a different temperature mode must be justified by the relevant factual material. In this case, the relevant section of the regulatory documentation should have indicated the rules for fixing the duration of this transportation mode. The proper quality of immunobiologicals, safety, and efficiency of their use were ensured by the "cold chain" system that must have been complied with at all four levels.

Sanitary-epidemiological regulations "Terms and Conditions of Transportation and Storage of Immunobiologicals" were mandatory for all legal entities, individual entrepreneurs, as well as citizens.[6] The safety and security of the immunobiologicals quality were ensured by a set of organizational, sanitary, and anti-epidemic (preventive) measures.

The "cold chain" consisted of four levels and provided optimal terms and conditions for transportation and storage at all stages of the immunobiologicals' movement from the manufacturer to the consumer. The first level was the delivery of immunobiologicals from the manufacturer to wholesale organizations, including the customs clearance stage. The second level included the storage of immunobiologicals by wholesale organizations and their delivery to other wholesale organizations,

pharmacies, medical organizations, and individual entrepreneurs. At the third level, immunobiologicals were stored by pharmacies, medical organizations, individual entrepreneurs, and delivered to medical organizations, their separate subdivisions, or other organizations (for example, medical offices of educational and other organizations), and sold in retail. The fourth level was the storage of immunobiologicals in medical organizations or their separate subdivisions (for example, district hospitals, dispensaries, polyclinics, and maternity hospitals), and other organizations (medical offices of educational and other organizations) where immunobiologicals were used.

The regulations set requirements for the equipment for the cold chain (equipment for transportation, storage equipment, equipment for temperature control of storage and transportation), general requirements for the organization of transportation and storage, and general requirements for the organization of measures in case of emergency. At all levels of the cold chain, the receipt and shipment of immunobiologicals by the organization were registered in a special register (form in Appendix 3 to the Regulations), where the entry stated the medicine manufacturer, its quantity (for vaccines and solvents for them – in doses), series, control number, expiration date, date of receipt (shipment), the supplier, thermal indicators and their identification numbers, as well as the full name (if available) of the responsible officer who carried out the registration. It is important to note that labeling of immunobiologicals necessarily included the release date on the primary and secondary (consumer) packaging (Article 46 of the Federal Law on Circulation of Medicines). It was necessary to make a record in the log about the instructions given to the responsible officer in the workplace about the compliance with the terms and conditions of storage and transportation, work with the refrigeration equipment, and work with registers.

In the log on the temperature in the refrigeration equipment (form in Appendix 2 to the Regulations), the followings were stated:

- Indicators of thermometers in the refrigeration (freezer) chambers (rooms) and refrigerators (freezers) where immunobiologicals were stored (at the third level – on a daily basis, twice a day).
- Facts of planned or emergency shutdown of the refrigeration equipment from the power supply, and breakdowns were registered.
- Violations of the temperature mode, the disconnection date, and time were registered.
- Indications of temperature indicators placed in refrigeration (freezer) chambers (rooms) and refrigerators (freezers) where immunobiologicals were stored, as well their personal number (on the third level – on a daily basis, twice a day) were specified.

All subjects related to the circulation of immunobiologicals must have developed and approved a Plan of Emergency Measures at the local level to ensure the cold chain in emergency situations. It is necessary to periodically (at least once a year) organize training on implementing the plan by involving all specialists and analyzing the performance of all the equipment. According to the training results, it was necessary to adjust the plan accordingly. The emergency plan should have clearly defined the followings:

- Procedure and means of notifying the authorized officials in the event of all possible emergencies in the organization, area, locality (fire, natural disasters, full or local power disconnection, and malfunction of refrigeration equipment).
- Procedures for ensuring the terms and conditions of storage and transportation of immunobiologicals and for appointing authorized officials.
- Locations and procedure of using backup equipment for the cold chain, including the equipment to control temperature and autonomous sources of lighting.
- Procedure for switching on and using the autonomous power supply system.
- Transport for the transportation of immunobiologicals, and the contact numbers of drivers.

Thus, careful compliance with the requirements for storage and transportation by all participants of the distribution chain ensured the proper quality, efficiency, and safety of using immunobiologicals.

Federal Law No. 449-FZ dated November 28, 2018, amended three federal laws on the issue of entering medicines into civil circulation. It was established that the new order of entry would take effect since November 29, 2019, and would cancel the current certification procedures (for vaccines, serums, toxins, serums, and immunoglobulins) and declaration (for allergens).

Each series of immunobiologicals manufactured in Russia or imported to Russia would be entered into civil circulation based on the license issued by the federal executive body that would perform the functions of control and supervision in healthcare. The license would be issued on the basis of the decision on the compliance of the series or the lot with the requirements established during state registration. The decision would be issued by the federal state budgetary institutions that have been subordinate to the Ministry of Health of Russia and the Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation and accredited in accordance with the legislation on accreditation in the national accreditation system. The procedures for issuing the license and the above decision, as well as its cost, have been defined by the Government of Russia.

It is necessary to note that the above license is not required for:

- Medicines intended for clinical research.
- Medicines intended for the examination of pharmaceutical products for the state registration.
- Unregistered medicines intended to provide medical care for the vital indications of a certain patient imported to Russia in accordance with the Federal Law on Circulation of Medicines.

In case of detecting a series or a lot of immunobiologicals that did not have the entry license in the civil circulation, the Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation would, in the prescribed manner, take a decision on terminating the civil circulation of such series or lots until they obtain the relevant license. It is relevant to note that the medicines entered into civil circulation before November 29, 2019, were subject to circulation before their expiration date (storage, transportation, distribution, sale, transfer, and use). Thus, the procedure for entering immunobiologicals into civil circulation has been more complex as compared to other medicines for manufacturers and holders of registration certificates.

Discussion

Promising initiatives of the Russian state policy related to the immunoprophylaxis were proposed by the Ministry of Industry and Trade of Russia within the Draft Strategy for the Development of the National Pharmaceutical Industry for the Period until 2030 (hereinafter referred to as the Pharma-2030 Project).[8] The Pharma-2030 Project showed considerable achievements in eliminating deadly diseases (plague, smallpox), a significant reduction in the incidence of serious childhood infectious diseases (whooping cough, diphtheria, parotitis, measles, rubella), and efficient protection of the population in the outbreaks of bacterial and viral infections (cholera, influenza, polio). At the same time, there has been a concern about the increase in the number of parents' refusals to vaccinate their newborns and children in their first years of life, which in the foreseeable future can cause considerable worsening of the epidemiological situation.

In the area of immunoprophylaxis, the state guaranteed the availability of prophylactic vaccines for citizens, free preventive vaccinations, included in the national calendar of preventive vaccinations (NCPV) and the calendar of preventive vaccinations for epidemic indications (CPV), in organizations of state and municipal health systems (Order of the Ministry of Health of Russia No. 125n dated March 21, 2014). It is necessary to note that 72 % of the vaccine market included NCPV purchases at the expense of the federal budget, 26 % of CPV purchases are at the expense of regional budgets, and only 2 % of the market contained commercial purchases. Today, the national prophylactic vaccination calendar includes 12 diseases. Over the recent five years, vaccines against hemophilic and pneumococcal infections have been included in it. Within NCPV, 22 immunobiologicals (vaccines) were purchased, including 18 vaccines that were purchased from a single supplier – JSC "National Immunobiological Company" (Order of the Government of Russia No. 714-r dated April 23, 2018). Funding for the centralized procurement within the national prophylactic immunization calendar increased from RUB 5.6 billion rubles in 2012 to RUB 15.8 billion in 2018.

It is necessary to pay special attention to the measures of reducing the injection load and providing innovative vaccines for newborns and children in the first year of life. Order No. 175-n of the Ministry of Health of Russia dated April 13, 2017, established that the children from risk groups could be vaccinated or re-vaccinated with immunobiologicals for the immunoprophylaxis of infectious diseases containing combinations of vaccines intended for appropriate age periods.

The Pharma – 2030 Project specified the problem that the NCPV did not cover a number of infections found in the calendars of other countries, in particular, against hepatitis A, meningococcal infection, human papillomavirus, chickenpox, and rotavirus infection. In order to expand the NCPV by 2020, it is planned to additionally introduce vaccination against rotavirus infection and chickenpox into the national immunization calendar. The attention has been paid to the calculations of the annual economic damage caused by the rotavirus infection, which is above RUB 6.8 billion, and the human papillomavirus (hereinafter referred to as HPV) that is above RUB 20 billion. According to the experts, it would be possible to avoid most of the costs by vaccination and to prevent over 5,000 deaths caused by cancer diseases associated with the HPV. Moreover, the prevention of diseases of the reproductive system with young women can give life to 1,350 children per year.

The Ministry of Industry and Trade of Russia has noted that trends in the vaccine market have been characterized by the movement of the global industry towards the development and production of new generation vaccines including polyvalent vaccines, recombinant vaccines created by using genetically modified cell cultures, short peptide vaccines, DNA vaccines that do not have a protein component, and other agents characterized by higher efficiency and safety. Much attention has been paid to both the quality of production capacities and the quality of vaccines.

In order to ensure the systematic approach for ensuring the obligations under the vaccination calendar, it is necessary to develop an interdepartmental national program for the development of vaccination and the local production of modern vaccines. In particular, the attention has been paid to both the provision of domestic vaccine needs with locally manufactured medicines, and the increase in the export potential of vaccines by 2030 for the needs of the World Health Organization, the market of EEU, and the third countries. According to the Ministry of Industry and Trade of Russia, the improvement of the interaction between Russian competent departments at the intergovernmental level, as well as the cooperation with the WHO, UNICEF, and international charitable organizations would assess the export potential of domestic manufacturers for the needs of foreign countries and the international health care system.

According to the authors, the development of the immunobiologicals' market in Russia would be associated with the improvement of sanitary-epidemiological legislation, preferences for domestic manufacturers as a part of the development strategy of the national pharmaceutical industry, as well as changes in the regulation of public procurement, including the establishment of the national institute of medicines interchangeability. The EEU Common Market for Medicines would have positive impacts on the development of domestic

export and import interactions within the regional-integration relations.[9-13]

Conclusion

Subjects of the medicine circulation in the Russian pharmaceutical market must responsibly comply with the requirements for all stages of the immunobiologicals circulation. This year manufacturers and holders of registration certificates must solve tactical tasks in accordance with the new procedure for introducing immunobiologicals into circulation. It is necessary to understand the areas of development of the domestic industry in the field of biological products and immunoprophylaxis in order to determine the strategic focus of pharmaceutical and biotechnological companies.

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