DEVELOPING THE SYSTEM OF STATE CONTROL OF DRUG QUALITY THROUGH FORMATION OF COMPETENCE CENTERS IN FEDERAL LABORATORIES OF THE INFORMATION CENTER FOR EXPERTISE, ACCOUNTING AND ANALYSIS OF CIRCULATION OF HUMAN MEDICINAL PRODUCTS OF THE FEDERAL SUPERVISORY AGENCY FOR HEALTHCARE OF RUSSIA

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State control over the drug quality is a key component of the healthcare system aimed at provision of patients with safe and effective medicinal products [1]. Stable development of this direction was closely associated with update of testing laboratories, which performed the function, and was characterized as a stable growth of laboratory competencies in the field of not just implementation of new analytical methods, but also in the systemic approach to improvement of skills and knowledge of personnel directly involved in laboratory research. A common approach reflected in accreditation criteria for compliance with GOST ISO 17025 means that the testing laboratory has a plan for internal and external education. However, conventional attitude to this issue does not lead to the desired practical effect. Then the laboratory is urged to find additional ways of development. Formation of competence centers by a certain vector of knowledge on the basis of testing centers can be a perspective option of the systemic approach to updating skills of the personnel. The Yaroslavl branch of the Information Center for Expertise, Accounting and Analysis of Circulation of Human Medicinal Products of the Federal Supervisory Agency for Healthcare and basic department of innovative pharmacy of the Yaroslavl State Medical University that successfully uses the basis can serve as examples of such an approach.

Keywords: laboratory of the Federal Supervisory Agency for Healthcare, basic department of innovative pharmacy, HPLC, Raman spectroscopy, GLP

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РАЗВИТИЕ СИСТЕМЫ ГОСУДАРСТВЕННОГО КОНТРОЛЯ КАЧЕСТВА ЛЕКАРСТВЕННЫХ СРЕДСТВ ЧЕРЕЗ ФОРМИРОВАНИЕ ЦЕНТРОВ КОМПЕТЕНЦИЙ В ФЕДЕРАЛЬНЫХ ЛАБОРАТОРИЯХ ФГБУ «ИМЦЭУАОСМП» РОСЗДРАВНАДЗОРА

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Государственный контроль за качеством лекарственных препаратов является одним из основополагающих элементов системы здравоохранения, направленным на обеспечение пациентов безопасными и эффективными лекарственными препаратами [1]. Устойчивое развитие данного направления неразрывно связано с совершенствованием испытательных лабораторий, осуществляющих данную функцию, и выражается в устойчивом увеличении компетенций лабораторий не только в области внедрения новых аналитических методов, но и в системном подходе к улучшению навыков и знаний персонала, непосредственно вовлеченного в процесс проведения лабораторных исследований. Общепринятый подход, отраженный в критериях аккредитации на соответствие ГОСТ ИСО 17025, предусматривает наличие в испытательной лаборатории плана как внешнего, так и внутреннего обучения, однако зачастую формальное отношение к данному вопросу не приносит желаемого практического результата, что побуждает лабораторию искать дополнительные пути развития. Одним из перспективных вариантов системного подхода к совершенствованию навыков персонала может стать формирование центров компетенций по определенному вектору знаний на базе испытательных центов. Примером такого подхода может стать Ярославский филиал ФГБУ «ИМЦЭУАОСМП» Росздравнадзора и базовая кафедра «инновационной фармации» Ярославского Государственного медицинского университета, успешно функционирующая на его базе.

Ключевые слова: лаборатория Росздравнадзора, базовая кафедра инновационной фармации, ВЖЭХ, Раман-спектроскопия, GLP

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The Information Center for Expertise, Accounting and Analysis of Circulation of Human Medicinal Products of the Federal Supervisory Agency for Healthcare is empowered to conduct tests of quality of medicinal products to detect their compliance with the requirements of pharmacopoeia articles included into the valid edition of the national Pharmacopoeia and Pharmacopoeia of the Eurasian Economic Union as a part of the state task. Twelve equipped laboratory complexes located in Moscow, Krasnoyarsk, Rostov-on-Don, Kazan, Tambov, Gudermes, Kursk, Stavropol, Simferopol, Khabarovsk, Saint-Petersburg and Yekaterinburg formed part of a budgetary institution until March 2021. However, a new

Fig. 1. Solemn opening ceremony of the Yaroslavl branch of the Information Center for Expertise, Accounting and Analysis of Circulation of Human Medicinal Products of the Federal Supervisory Agency for Healthcare.

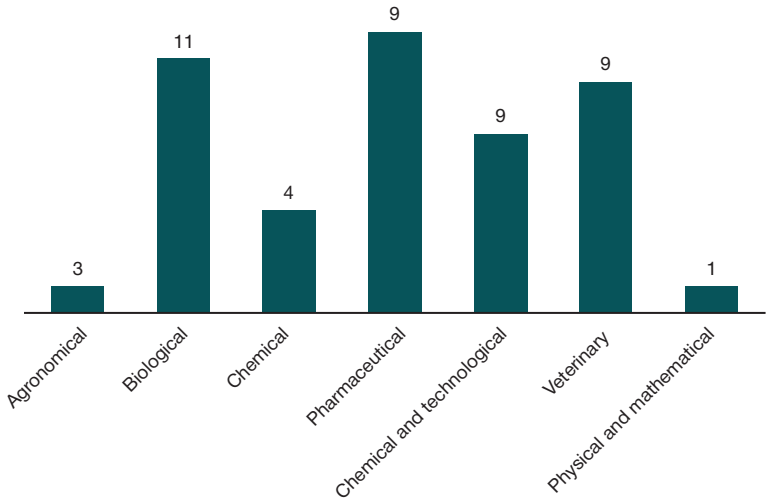

Fig. 2. Diagram of distribution of laboratory employees by their education

thirteenth laboratory was opened in Yaroslavl in March 2021 (fig. 1).

A newly opened laboratory, which is a joint investment project of the Federal Supervisory Agency for Healthcare and Yaroslavl region, was the largest one in the structure of the institution. Total area of the building and adjacent structures was over 7,000 square meters. The complex includes analytical and microbiological laboratories, laboratory of control of quality of immunobiological medicinal preparations, pharmacological laboratory and mass spectrometric center.

Subsequently, a group of Raman spectroscopy and perspective developments working on express methods of analysis of medicinal preparations, including methods of control of medical gases, moved from Kazan to Yaroslavl. The total staff size of the laboratory is 77 people. They are mainly professionals with pharmaceutical, chemical, biological and higher veterinary education (fig. 2). Their average age is 37 years.

Employees of the lab are represented both by young specialists from the Yaroslavl region, and foreign specialists.

The center is equipped with the most up-to-date equipment and engineering systems. They can be used to solve pressing issues and face the future with confidence.

1. BASIC DEPARTMENT OF INNOVATION PHARMACY

Launching of the laboratory was accompanied by signing of an agreement between the Information Center for Expertise, Accounting and Analysis of Circulation of Human Medicinal Products of the Federal Supervisory Agency for Healthcare and Yaroslavl State Medical University. It was marked by the functioning of the basic department of innovative pharmacy on the basis of the branch. The most important activities of the department included tasks of career orientation for students and advanced training of the lab employees and professionals who desire to gain new knowledge through participation in the professional training programs. By October 2022, two educational programs such as ‘Identification of pharmaceutical substances and ready-made medicinal products using non-destructive methods spectral methods of express analysis such as near infrared and Raman spectroscopy. Incoming control over production’ and ‘High-performance liquid chromatography: basis of the method, measurement technique, practicum’ have been developed. Another program named ‘Organization and conduction of preclinical trials in accordance with the national and international rules of GLP’ has been developed and approved as well. The first theoretical

and practical classes were conducted using the approved programs. The results were utilized to take a decision on placement of the theoretical part on the digital educational platform of the Information Center for Expertise, Accounting and Analysis of Circulation of Human Medicinal Products of the Federal Supervisory Agency for Healthcare.

Supporting career orientation, the students of the Yaroslavl State Medical University were prepared to defend their theses with regular excursions and practical training that make the students familiar with the activity of the Federal Supervisory Agency for Healthcare in the field of state control of quality of medicinal agents.

The innovative pharmacy basic department became a solid foundation to establish a center of competencies on the basis of the branch that provided the necessary impetus. The impetus was aimed at the systematic development of professional reputation of the newly formed laboratory complex.

2. CENTER OF MASS SPECTROMETRIC ANALYSIS

Due to high cost of equipment, expendable materials and reagents and very high requirements to personnel competence, mass spectrometry failed to become generally recognized during standard procedures of testing the quality of medicinal products. In the majority of pharmacopeial articles to determine product-related impurities, HPLC detectors are used such as a UV–Vis spectrophotometer, fluorometric, refractometric and — in some cases — evaporative light-scattering, conductometric and amperometric detectors. However, when extremely high sensitivity and high selectivity are required, it is difficult to find a detection method, which could be as good as mass-spectrometry coupled with HPLC or GC. The idea was clearly demonstrated while detecting genotoxic mixtures of nitrosamines in preparations of sartans, ranitidine and metformin.

The center was equipped with various types of mass-spectrometers such as HPLC high resolution Q-ToF MC/MC, which allows to deal with complex tasks of protein molecule characterization, including spectrum measurement of intact proteins (fig. 3) and peptide mapping, with the ultra-sensitive triple quadrupole MS/MS system used in qualitative analysis, GC–MS system intended to determine pesticides in medicinal plant material, and inductively coupled plasma mass spectrometer to determine elemental impurities in pharmaceutical substances and excipients.

The center is currently the only separate subdivision of that type in testing labs that perform quality control of medicinal products. Over 25 methods, including methods described in general monographs of the SP of Russia, have been developed and validated during a year and a half.

The center employees are highly qualified in this field of knowledge and actively participate in Russian and international research conferences.

3. THE GROUP OF RAMAN SPECTROSCOPY AND PERSPECTIVE DEVELOPMENTS

The group concentrates mainly on the development of novel methods of quality control of medicinal products including non-destructive express methods and control methods of medical gases. As far as the last ones go, the group uses combined light scattering spectroscopy (Raman spectroscopy), which allows to check the validity of liquid medicinal products, powders and pharmaceutical substances, and — for some products — quantitative analysis in relation to the original specimen.

Scientific interests of the group include not only instrumental method documentation, but also development of new mathematical algorithms to process and analyze spectral data and software, which can effectively deal with novel algorithms [2,3]. The ways of developing reference spectral models used by the Federal Supervisory Agency for Healthcare represent a unique development and have been registered in the Russian Federation.

Software created by the group specialists is based on the use of cloud technologies. They unite several laboratories into one network.

Many years of work within this group resulted in the development of Mini-Ram 532 software and hardware system (fig. 4) actively implemented by the Federal Supervisory Agency for Healthcare within mobile labs to control quality of medicinal products [4–6].

Development of methods of analysis of medical gases, including medical oxygen, represents another activity area of the group. A method of control of medical oxygen quality with gas chromatography and PIA portable gas chromatography complex has been developed (fig. 5). The complex was created jointly with the Russian company based in S. P. Korolev Samara Research University. The method was metrologically certified by the Ural Research Institute of Metrology.

The developed method is used to perform oxygen analysis during several minutes practically by all principal indicators (assess oxygen content, check admixtures of carbon monoxide and dioxide). The method was introduced into the

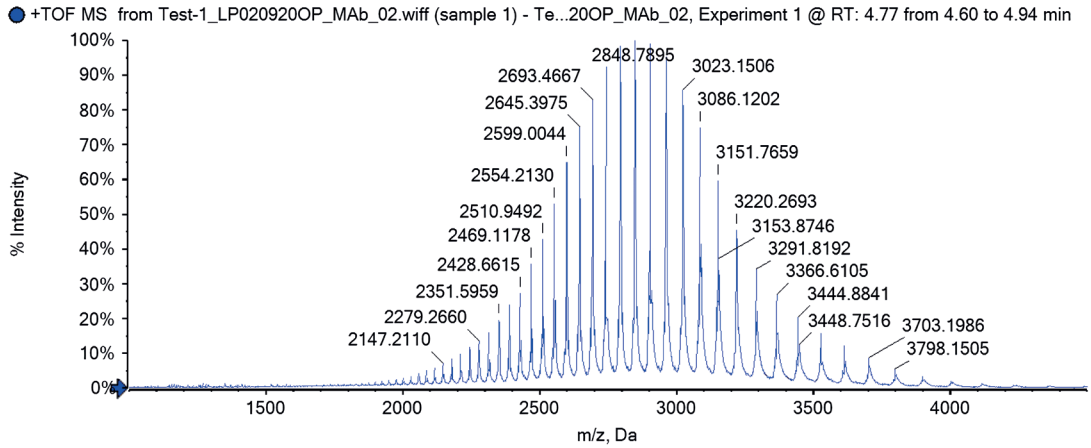

Fig. 3. Mass spectrum of pertuzumab monoclonal antibody

Fig.4. Mini-Ram 532 software and hardware system (SHS), general view

Fig. 5. PIA gas chromatography complex, general view

Pharmacopoeia of Russia in 2020. This allowed to reduce the time spent on analysis of one oxygen series from one day to one hour minimum, including all preparatory works associated with sampling. It is especially important during pandemic when consumption and production of oxygen is increased several hundred times.

Moreover, the method can be used in the mobile lab owing to compactness of the equipment. This addresses the problem of transportation of dangerous cargo including oxygen bottles to the lab and their storage. All branches of the Information Center for Expertise, Accounting and Analysis of Circulation of Human Medicinal Products of the Federal Supervisory Agency for Healthcare are supplied with this equipment, and specialists underwent necessary training.

4. PARTICIPATION IN INTERNATIONAL EXPERT COMMITTEES

International activity is an essential part of formation of high competence regarding the issues of quality control of medicinal products due to harmonization of principles and approaches at the level of national and supranational pharmacopeial committees.

Specialists from the testing lab of the Yaroslavl branch of the Information Center for Expertise, Accounting and Analysis of Circulation of Human Medicinal Products of the Federal Supervisory Agency for Healthcare are active participants of expert working groups within the European (EDQM), groups 10A, 9, 9G, and American Pharmacopoeia. They also represent interests of the Russian Federation in the International Council on ICH Harmonization.

Several analytical methods included into the valid edition of the European Pharmacopoeia were developed, validated and verified in continuous cooperation with the European Directorate for the Quality of Medicines.

5. CERTIFICATION OF CELL BANKS OF PRODUCERS

The Yaroslavl branch was the third branch within the Yaroslavl branch of the Information Center for Expertise, Accounting and Analysis of Circulation of Human Medicinal Products of the Federal Supervisory Agency for Healthcare of Russia. The laboratory that controls quality of immunobiological medicinal products is included in its structure. This subdivision is intended for quality tests of such medicinal products as vaccines, sera, toxins, anatoxins, monoclonal antibodies, etc. However, specialists quickly mastered a new direction, complex attestation of cell banks of producers.

Requirements to the system assessing quality of cell cultures during manufacture of immunobiological medicinal products are determined considering the need in substrate safety maintenance [7]. Testing methods of cell cultures are determined in the State Pharmacopoeia of Russia XIV (GMP. 1.7.2.0011.15 Requirements to cell culture substrates used in manufacture of immunobiological medicinal products, GMP. 1.7.2.0006.15 Test of viral vaccines for foreign agents) and Decision of the Council of the Eurasian Economic Commission as of November 3, 2016 No. 89 ‘Concerning approval of the Rules of Testing Biological Medicinal Products of the Eurasian Economic Union’.

The majority of necessary methods have already been presented in the lab. However, when the lab started functioning, some specific methods were lacking. Their urgent introduction was required. These methods included genetic sequencing and karyotyping.

Current capabilities of the lab allowed to conduct attestation both of the main, and working cell banks. Until recently, this could have been done in foreign labs only.

The lab employees developed new approaches and methods that will form the basis of theses to be defended at the innovative pharmacy department.

6. SCIENTIFIC ACTIVITY

The innovative pharmacy basic department was the essential element of the lab complex that allowed to amend developmental vectors of the lab and specialists by means of their participation in scientific developments and implementation of possible defense of PhD and doctoral theses.

Scientific researches in the field of bioanalytical studies associated with creation of new assay methods of medicinal products in the blood of patients using the surface-enhanced Raman spectroscopy and in the field of pharmaceutical chemistry associated with creation of express methods of screening the quality of medicinal products and medical gases are actively carried out. 4 topics of PhD theses have been approved.

Achievements in the field of new developments are being actively published both in Russian, and foreign scientific journals.

7. CONCLUSION

Thus, establishment of competence centers with a number of directions related to quality control of medicinal products gives a possibility to move from a simple model of formal reproduction of methods from monographs to a more complicated model. The last one includes a set of activities aimed at formation of high professional reputation of the lab. This is confirmed by an increased amount of consultation and information services in the field of development and validation of new methods provided by the branch (5.074 hours in 2022 as compared with 1.086 hours in 2021).

One of the most important aspects of the selected strategy of the branch development as a competence center was the basic innovative pharmacy department. It was a bridge between the academic environment to the practical use of knowledge accumulated during decision of scientific tasks, on the one hand, and aid in career orientation, on the other hand.

Subsequent plans of the lab development include implementation of a greater number of unique directions associated with the quality testing of medicinal products, attestation of standard samples and working with radiopharmaceuticals.

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