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И РОССИЙСКОГО НАЦИОНАЛЬНОГО ИССЛЕДОВАТЕЛЬСКОГО МЕДИЦИНСКОГО
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In the 21st century, the rapid advance of space programs raises ethical concerns about the consequences of exploring and exploiting space resources. The concept note of the World Commission on the Ethics of Scientific Knowledge and Technology (COMEST) on the ethical considerations on space exploration and exploitation adopted in August 2024 states that "the international community is now in need of developing ethical principles for space exploration and exploitation that complement currently existing outer space treaties". Key areas for future ethical regulation of space projects include prospects for commercial developments, space tourism programs, mining, and deep space exploration to study exoplanet atmospheres and search for terrestrial planets. Space exploration provides important knowledge that improves the quality of life and has a technological and innovative impact on society. The "inspiring factor" of space research is crucial for motivating future generations of scientists to develop science. However, it must be borne in mind that human activities pose significant risks to both near-Earth space and Earth's ecosystems. The scale of space ethics proposed by COMEST will help systematize information about ethical uncertainty factors, risks and consequences of risks associated with initiatives in space exploration and exploitation.

Key words: space research, UNESCO, The World Commission on the Ethics of Scientific Knowledge and Technology, space ethics, ecology

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ЭТИЧЕСКИЕ АСПЕКТЫ И ПЕРСПЕКТИВЫ ИЗУЧЕНИЯ И ОСВОЕНИЯ КОСМИЧЕСКОГО ПРОСТРАНСТВА

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Темпы развития космических программ в XXI в. ставят перед исследователями вопросы этического характера, связанные с последствиями изучения и освоения ресурсов космоса. В принятой в августе 2024 г. Всемирной комиссией по этике научных знаний и технологий (КОМЕСТ (COMEST)) в концептуальной Записке «Об этических соображениях при исследовании и эксплуатации космоса» отмечается, что «международное сообщество в настоящее время нуждается в разработке этических принципов исследования и эксплуатации космического пространства, которые дополняют существующие в настоящее время договоры по космосу». Задачи этического регулирования космических проектов должны охватывать перспективы развития коммерческих разработок, программы космического туризма, добычу полезных ископаемых, исследования дальнего космоса, в том числе для изучения атмосфер планет вокруг других звезд и поиска планет земного типа. Изучение космической среды дает важные знания, улучшающие качество жизни, расширяет технологическое и инновационное влияние на социум. Важен и «вдохновляющий фактор» космических исследований, побуждающий новые поколения ученых заниматься развитием науки. При этом необходимо учитывать наличие рисков влияния деятельности человека на околоземное пространство и непосредственно на экосистему Земли. Предложенная КОМЕСТ шкала космической этики поможет систематизации информации об этических факторах неопределенности, рисков и последствий рисков, связанных с инициативами в исследовании и эксплуатации космоса.

Ключевые слова: космические исследования, ЮНЕСКО, Всемирная комиссия по этике научных знаний и технологий, космическая этика, экология

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The first steps in 20th-century space exploration spurred bioethical questions about human expansion beyond biosphere. The Treaty on principles governing the activities of states in the exploration and use of outer space, including the moon and other celestial bodies (Moscow-Washington-London, January 27, 1967) [1], Agreement on the rescue of astronauts, the return of astronauts and the return of objects launched into outer space (December 19, 1967) [2], Convention on international liability for damage caused by space objects (Moscow — London — Washington, March 29, 1972) [3], Convention on registration of objects launched into outer space (New York, January 14, 1975) [4] and a number of other international documents [5] were adopted.

In the 21st century, ethical issues of space exploration turned into necessary and urgent tasks of civilizational importance due to the intense progress of science and technology.

THE RELEVANCE AND TASKS OF FORMING SPACE ETHICS PRINCIPLES

When the world community recognized that it was necessary to develop ethical regulators for space programs, a decision was adopted on August 24, 2009 during the 182nd session of UNESCO that enlarged the powers of the World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), an advisory body and forum of reflection that was set up by UNESCO in 1998.

"To improve the ability of COMEST to advise UNESCO on ethics of science, nanotechnologies, and ecological ethics as expected, the structure of COMEST should be enhanced to be similar to other expert advisory bodies, like the International Bioethics Committee" [6].

The International Bioethics Committee (IBC) was established in 1993. It prepares documents to define priorities for international bioethical discussion. The International Bioethics Committee (IBC) is related to the Intergovernmental Bioethics Committee (IGBC) and the World Commission on the Ethics of Scientific Knowledge and Technology (COMEST).

At the 13th (Ordinary) Session of COMEST in September 2023, the Working Group established by the Commission adopted the concept note of the World on the Ethical Considerations on Space Exploration and Exploitation in August 1, 2024 under the working program for 2024–2025 [7].

The ethical considerations related to space exploration and exploitation proposed by COMEST are based on previous Commission documents such as the Report on the Ethics of Space Policy (2000), the Report on the Ethics of Water Resources: Ocean, Freshwater, Coastal Areas (2018), the Report on the Ethics of Land Use (2021), and the Report about the Ethics of Climate Engineering (2023).

It is stated in the introduction to the concept note of COMEST 2024 that the humanity is entering a new era of space exploration and exploitation and plans to establish permanent robotic and human bases on the Moon, asteroids and Mars, conclude Lunar international treaties and allow the private sector to fully lead commercial space missions. Thus, "the international community is now in need of developing ethical principles for space exploration and exploitation that complement currently existing outer space treaties".

Stating that "humanity has benefited enormously from the exploration of space in the last 60 years" and that international cooperation is essential for space exploration, COMEST suggests that the following ethical issues have to be solved:

- the consequences of private, commercial and public efforts in space exploration and exploitation, in terms of responsibility to present and future generations;
- ethical concerns of the geopolitical implications of the "race for permanence in space" and equal access to space for all countries, including space governance, space militarization, space tourism, and potential environmental harm to space.

According to COMEST, space exploration has entered "a breakthrough era" owing to the development of space projects, space tourism, space mining and human permanent presence in space in 2025 to 2100. Active lunar exploration is planned as well. The Artemis Initiative (2010) led by the NASA that aims to land astronauts on the Moon is one example [8].

The international Mars exploration programs are found perspective as their goals include permanent missions and potential terraforming to ensure long-term human presence on Mars and protection from solar and cosmic radiation.

Astrophysical studies of far space are highly perspective. They include the ones using the James Webb Telescope (JWST) that opened the doors to distant worlds around other stars and made the search for Earth-like planets possible.

Developing ethical and sustainable space regulations must account for future technology associated with resource extraction and profit generation. This requires concluding contracts and creating a global legal infrastructure for sustainable ethical cooperation resulting in competition between the private and public sectors over the next decades that will likely fuel a self-sustaining space industry.

Defining the modern state of space ethical regulation, COMEST states that the existing international treaties and associated agreements deal with space exploration problems and risks. Some of these agreements may require revision to bring them up to date in this new era of space ethics. The question of environmental problems and the use of physical resources in space remains largely open. Efforts are being taken to solve the issue now. In particular, the UN Committee on the Peaceful Uses of Outer Space (COPUOS), established on December 12, 1959, works on international cooperation for space debris management.

Modern "space ethics" must correlate 20th-century principles of space explorations with contemporary advantages and risks.

According to COMEST, the advantages definitely include technological and scientific effect of space exploration on the life of a human including the use of numerous items in our everyday life.

Social achievements and benefits that improve daily life consist of enhanced satellite communications and telecommunications, global positioning, food and fisheries production, medical developments and achievements in weather forecasting and climate monitoring, management of forest, natural disasters, and pollution, as the data are vital for environmental conservation and efforts to mitigate the effects of climate change. Thus, space exploration provides people with essential knowledge and possibilities to be used by the society.

"Space exploration has also contributed to many diverse inventions used in everyday life, from solar panels to heart monitors, from cancer therapy to lightweight materials, rechargeable batteries, miniaturization of multiple devices and from water purification systems to improved computing systems, environmental studies and global search and rescue systems".

As stated in COMEST, the "inspiring factor" of space research is its power to inspire new generations of scientists to develop science, technology, mathematics and engineering, as well as offer unique and innovative solutions for numerous social problems.

Significant risks in human spaceflight include cosmic radiation, the physiological effects of weightlessness leading to muscle and bone loss and osteoporosis, hearing loss due to the constant exposure to the noise from orbital station equipment. The inability to prevent these negative consequences has led to the use of robotics in space exploration systems. In the future, maximum scientific and economic benefits are expected from the partnership between people and robots. In this regard, comparing the possible risks and benefits of human participation in extraterrestrial resource development is a key task of space ethics.

Environmental risk group should include the impact of human activities on near-Earth space and the Earth's ecosystem. Accumulation of space debris in Earth's orbit poses a significant risk to active spacecraft and creates a direct physical risk on Earth's surface due to uncontrolled descent of debris. Rocket launches can damage the atmosphere and the ozone layer. Ground-based facilities like spaceports influence local ecosystems.

The expansion of space missions in the future will increase risks to planetary environmental protection. The possible depletion of space resources as a result of their uncontrolled use is the major long-term ethical concern that should be recognized now to exterminate the dilemmas of advantages and risks of cost-effective space exploration.

The COMEST study stresses that key ethical aspects of space exploration and exploitation should be determined "since intuitive principles applicable on Earth may not be appropriate outside the planet".

According to COMEST, basic principles of space ethics include equative justice and fairness, nonmaleficence and beneficence and respect and the precautionary principle.

Justice and fairness are basic ethical principles in space exploration that should be open and inclusive for both individuals, and countries. The requirement primarily concerns distribution and re-distribution of space resources depending on the research potential of different countries.

The problem can be solved through a fairly balanced participation in space projects under due consideration of the interests of the countries without necessary resources for space exploration. The same goes for the educational resources used to exchange knowledge and build the capacity of the countries interested in space programs, including the interests of future generations.

Space research participants should be informed of possible risks and harm mitigation efforts. The principles of nonmaleficence and beneficence should be used in the context of multispecies ethics, while sending animals to space and as astrobiological principles to protect any possible habitats for life.

Balancing space exploration with preservation is crucial not to compromise the space environment for current and future use. International agreements should provide solutions to issues related to the use of space resources, including in terms of increased competition and risk of conflict.

Ecological ethics in space should rest upon the requirements to environmental protection, space preservation and restoration. Space activity can be related to protection of space from human intervention (results of space debris accumulation).

The principles of cooperation in space offered by COMEST include requirements to prevention of conflicts, including in the sphere of commercialization, which are possible due to expanded participation in space programs by countries and individuals, fair and equal use of resources, interaction in the area of environmental protection, regulation of technological achievements in safety standards at the international, regional and national levels of cooperation.

Preserving the peaceful nature of space exploration is crucial. This also applies to the potential for finding extraterrestrial life. The human desire for peaceful coexistence in space is delivered through messages sent beyond the Solar System by the Pioneer-10 and Pioneer-11 probes [9]. Any international agreement on the exploration and exploitation of outer space must meet the criteria of transparency and ensure access to reliable monitoring technologies for all interested parties.

Stating that the development of space research and space exploration projects requires updated ethical standards, the World Commission on the Ethics of Scientific Knowledge and Technology has adopted recommendations for peaceful ethical space exploration. In addition to the general provisions for international cooperation, a balanced assessment of potential benefits and risks, equal access and allocation of resources, including knowledge and innovation, transparency and accountability, COMEST proposed the space ethics scale as a communication tool to convey multi-level information and facilitate dialogue among all participants.

The space ethics scale will make it possible to systematize information about the ethical factors of uncertainty, risks and consequences of risks associated with initiatives in space exploration and exploitation. The structure of ethical factors can be used in correlation with natural disaster warning systems, indicators of possible UV exposure and damage to the ozone layer, monitoring of near-Earth space and other safety criteria. Ethical criteria will become a tool for adapting to the changing needs of space exploration and exploitation.

Humans have ethical obligations towards space and space resources, particularly for the future of the field. The obligations should be implemented based on a wide axiological range of economic, ecological, esthetic and other values.

Space ethics requirements should become the basis for legal standards in the development of space projects. Ethical factors shape the progress of space biology, space medicine, and space psychology, as well as the development of space programs involving humans, not only through experimental determination of its adaptive capabilities, but also using a broader understanding of these disciplines as **human sciences** that explore both physiological and spiritual resources of humans [10].

COOPERATION IN THE FIELD OF SPACE EXPLOITATION

On October 27, 2017, the first UNESCO Medal on Space Science was awarded at the organization's headquarters in Paris to recognize achievements in space exploration. The award was given to Valentina Vladimirovna Tereshkova. When receiving the UNESCO medal, the first female cosmonaut emphasized that "space should be an arena of peaceful cooperation" [11].

The International Space Station (ISS) is a prime example of successful international partnership in space exploration, involving the space agencies of Russia (Roscosmos), the United States (NASA), Japan (JAXA), Canada (CSA), and Europe (ESA). Since its first module launched in 1998, it has become a multipurpose space research laboratory where these agencies cooperate on national space scientific programs [12].

The fight against space debris is being coordinated. According to the Interagency Space Debris Coordination Committee (IADC) for 2023, over 30,000 pieces of space debris larger than 10 cm and about 900,000 objects larger than 1 cm are concentrated in low-Earth orbit (LEO). In July 2023, The Office of Space Trade has approved the Traffic Coordination System for Space roadmap, and the European Space Agency announced its Zero Debris Charter to achieve zero debris by 2030 [13].

On June 16, 2021, Roscosmos and China National Space Administration (CNSA) held a joint session to present the roadmap for the International Lunar Research Station (ILRS). This project aims to create a research facility on the Moon's surface or in orbit to conduct multifunctional scientific research and support future human presence.

Russia together with Belarus, Kazakhstan and Armenia develop cooperation in the space sector. An international partnership is continuing to utilize several neutron instruments such as the HAND on NASA's Mars Odyssey, the LAND on NASA's Lunar Reconnaissance Orbiter (LRO), and the DAN on NASA's Curiosity rover, as well as the Spektr-RG and Konus-Wind projects.

Russia and Europe continue their cooperation through numerous projects including Soyuz at the Guiana Space

Center (Russia-France), ExoMars-2016, Bepi-Colombo, and Mars Express projects of Roscosmos and the European Space Agency (ESA). Russia has developing space partnerships with Spain (World Space Observatory-Ultraviolet), Germany (Spektr-RG), Brazil, Nicaragua, and the South African National Space Agency (SANSA) [14].

The Russian Federation supports international cooperation and remains one of the leaders in space programs. Russian cosmonaut Valery Vladimirovich Polyakov holds the record for the longest single spaceflight, with a duration of 437 days, 17 hours, 58 minutes, and 17 seconds aboard the Mir space station from January 1994 to March 1995. Russian cosmonaut Gennady Ivanovich Padalka holds the world record for total time in orbit with a duration of 878 days, 11 hours, 29 minutes, and 36 seconds during 5 flights, registered by the International Aviation Federation (FAI) in September 2015 [15].

Space monitoring is vital for the successful development of terrestrial resources, including the ones in the Arctic region [16]. According to the leading experts of the Space Research Institute of the Russian Academy of Sciences, Arctic exploration is a major driver of its 21st-century development for Russia [17]. Mutual international cooperation to ensure space exploration and exploitation and to use space technology for terrestrial resource management based on pressing values of the civilization can be possible if the world community participates in the bioethical discussion of vital issues of science and technology development.

CONCLUSIONS

Sustainable principles for the ethical regulation of space programs must balance human spaceflight risks and benefits with environmental factors.

According to the World Commission on the Ethics of Scientific Knowledge and Technology, basic principles of space ethics include equative justice and fairness, nonmaleficence and beneficence and respect, and the precautionary principle. They form the basis of the space ethics scale as a communication tool to convey multi-level information and facilitate dialogue among all participants.

Space ethics requirements should become the foundation for legal standards in the development of space projects. Development of space programs involving humans is possible due to the progress of space biology, space medicine, and space psychology, and also using a broader understanding of these disciplines as human sciences that explore both physiological and spiritual resources of humans, and their ability to adaptation in a new physical and cultural reality.

The future of space research also depends on society developing a mature and scientifically informed view of space exploration, moving beyond simplistic portrayals common in popular culture. In this aspect, scientific and educational work, museum and media projects reflecting real achievements in the space industry can substantiate humanistic values in the study of the universe.

International cooperation in space is crucial for activities such as maintaining the ISS, combating space debris, planning future projects like a lunar station, and using space technology for Earth resource exploration, including in the Arctic.

Bioethical discussions, addressing a wide range of issues from technological challenges to the humanistic values, are essential for implementing the goals of space exploration.

The COMEST concept note on ethical considerations highlights that “space is a hostile environment that will always pose challenges to human endurance and spirit”.

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THE FUTURE OF THE DIGITAL BODY: POSSIBILITIES AND CHALLENGES

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The presented study delves into the concept of the digital body within the context of modern technologies and their impact on the society, culture and personality. A digital body is defined as a representation of a physical body in virtual reality, augmented reality, and on other digital platforms. The article reviews opportunities for health support, self-expression, expansion of human experience, and social connections in the digital space provided by digital bodies. The authors also explore numerous challenges faced by the society when digital bodies are introduced. These include data safety, ethical dilemmas related to identity and privacy, as well as implications for mental health and social structure. The article makes predictions about the future of digital bodies stressing that an interdisciplinary approach is required to solve the arising issues. The aim of the analysis is to attract attention to the complex dynamic relationship between technology innovation and human experience, as well as to shape awareness about how digital bodies can transform our society within the next ten years.

Keywords: future of the digital body, technologies, artificial intelligence, virtual reality, biometric data, digital identity, ethics, security, privacy, health

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БУДУЩЕЕ ЦИФРОВОГО ТЕЛА: ВОЗМОЖНОСТИ И ВЫЗОВЫ

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Представленное исследование посвящено анализу концепции цифрового тела в контексте современных технологий и их влияния на общество, культуру и личность. Цифровое тело определяется как виртуальный аналог физического тела, который можно создать и развивать в виртуальной реальности, дополненной реальности и с помощью других цифровых платформ. В статье рассматриваются потенциальные возможности, которые предоставляет цифровое тело, такие как улучшение здоровья, возможности самовыражения, расширение границ человеческого опыта и развитие новых форм взаимодействия в цифровом пространстве. Однако наряду с этим авторы также обращают внимание на многочисленные вызовы, стоящие перед обществом в связи с внедрением цифровых тел. К числу таковых относятся вопросы безопасности данных, этические дилеммы, связанные с идентичностью и приватностью, а также последствия для психического здоровья и социальной структуры. Статья содержит прогнозы относительно будущего цифровых тел, подчеркивая необходимость междисциплинарного подхода к решению возникающих проблем. Проведенный анализ направлен на привлечение внимания к сложной динамике между технологическими инновациями и человеческим опытом, а также на формирование осознания о том, каким образом цифровые тела могут трансформировать наше общество в ближайшие десятилетия.

Ключевые слова: будущее цифрового тела, технологии, искусственный интеллект, виртуальная реальность, биометрические данные, цифровая идентичность, этика, безопасность, конфиденциальность, здоровье

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An introduction to the concept of the digital body is an important step that helps to understand how a human being interacts with technology in the modern world. A digital body can be defined as a representation of a physical body in a virtual environment, including anonymous and public data created and controlled using the technology [1,2]. It is an expression of personality that is formed through various digital platforms such as social networks, online services, and even devices that collect and analyze user data [3,4]. The problem contributing to the research of the digital body concept lies in the contradiction between the rapid integration of digital technologies into everyday life [5] and insufficient willingness of social, legal and technical institutions [6] to ensure safety, privacy and integrity of user's identity [7] in the digital environment [8]. This problem is connected to multiple interrelated challenges. Firstly, high volume of collected personal and biometric data, their aggregation and analysis through machine learning algorithms create risks of unauthorized access, leaks and misuse of information, which undermines trust in digital services. Secondly, blurred boundaries between virtual and physical identity result in subjective and ethical dilemmas such as transformation of self-awareness, possibility of manipulating behavior through personalized content, and difficulties in assigning legal responsibility for actions in mixed realities. Thirdly, the active use of VR/AR and remote digital platforms leads to social consequences such as risks of social isolation, dependence on virtual environments and decline of interpersonal skills, which negatively affects mental and physical health of some users. Fourthly, technical and infrastructural barriers such as insufficient availability of high-speed Internet and modern devices [9], as well as

disparate standards and regulatory approaches in different jurisdictions make it difficult to implement technologies evenly and safely [10]. When AI is used to manage the digital body, additional challenges are faced such as the need to ensure the transparency of algorithms [11], prevent bias, and explain the decisions that affect the personal aspects of people's lives [12].

The research background includes achievements of many authors and practitioners. In the 1990s and early 2000s, early works on online identity and avatars laid the theoretical foundations for understanding the digital self and the social effects of online self-expression [13]. Empirical studies on biometrics and health monitoring [14] have demonstrated that the digital body potential for preventive medicine and personalized care is high and simultaneously showed data vulnerabilities and the need for ethical standards [15,16].

Research in VR/AR and cybernetics has confirmed that immersive technologies can transform user perception and behavior [17], paving the way for pedagogical simulations and virtual clinics [18]. Negative effects with uncontrolled use have been recorded as well [19, 20]. Research in AI is focused on creating adaptive interfaces and decision support systems. At the same time, the number of publications and standards offering mechanisms for ensuring privacy, differential privacy, explainability of models and combating algorithmic discrimination is increasing [21]. Finally, interdisciplinary research on the social impact of digital platforms has identified ways to reduce misinformation, develop emotional intelligence, and improve digital literacy as key elements of increasing society's resilience to the negative effects of digitalization. The most promising ways to address these challenges include an integrated, multi-level approach combining technological, regulatory, educational, and social measures. Technical solutions involve introduction of data protection and cybersecurity standards, use of default privacy by design, data-level encryption, differential privacy in analytics, and limited retention of sensitive information. Development of transparent, explicable models, audit algorithms, and bias control mechanisms is critical for AI. Regulatory measures should include common principles to regulate processing of personal and biometric data, ensure international coordination of standards, and clear responsibility of platforms for user safety and correct use of data.

Educational and awareness-raising initiatives are focused on improving digital literacy, critical thinking skills, and emotional intelligence so that users can consciously manage their digital bodies and respond sustainably to risks. Socio-psychological interventions and support services are designed to detect and mitigate addictions early, preserve interpersonal skills, and support mental health of users. In addition, development of inclusive infrastructure and reduction of the technical gap should ensure equal access to safe technologies and reduce the risks of marginalization of certain groups. The purpose of the research is to comprehensively analyze the nature of the digital body, its historical development, modern manifestations and consequences of the integration of digital and physical spheres of life, as well as to develop multilevel recommendations and practices aimed at ensuring security, privacy, ethics and social sustainability of digital identity of users. It is assumed that achieving this goal will contribute to the informed formation of policies, standards and educational programs necessary for safe and inclusive development of the digital society.

The hypothesis of the study is formulated as follows: introduction of agreed technical standards for data protection and algorithmic transparency, accompanying these measures with adequate regulatory regulation and extensive educational programs on digital literacy and emotional intelligence turn the digital body management into a safer and more controlled process, which will reduce the risks of loss of privacy and manipulation, mitigating social and mental negative effects of digitalization and improving the quality of medical and educational services based on digital data.

MATERIALS AND METHODS

This research is based on an interdisciplinary approach that uses methods of theoretical analysis, systematic review and conceptual understanding to study the digital body and its interaction with modern technologies. The main goal was a comprehensive review of historical development, current manifestations, prospects of the digital body, related challenges and opportunities in various spheres of human activity.

A wide range of scientific sources, including monographs, articles in peer-reviewed scientific journals, conference materials, analytical reports and reviews from leading research centers and organizations in the field of information technology, sociology, philosophy, medicine, and education were used as research materials. Special attention was given to publications on digital identity, virtual and augmented reality, artificial intelligence, ethical aspects of digitalization, cybersecurity, and impact of technology on social, cultural and professional processes. Literature was searched and selected using leading scientific electronic databases.

The following research methods were used:

- System analysis: to study the digital body as a complex dynamic system combining physical, virtual and social aspects of human existence.
- Historical and genetic method: to trace the evolution of the digital body from early ideas of the virtual Self to modern complex configurations that occurred due to development of Internet technologies, social networks, VR/AR and AI.
- Comparative analysis: to compare different approaches to understanding and managing the digital body, and identify common trends and specific features of its manifestation in different fields (healthcare, education, social interactions, work).
- Conceptual analysis: to detail key concepts such as "digital body", "virtual reality", "augmented reality", "artificial intelligence", "privacy", "security", and identify the relationships between the concepts.
- Ethical reflection: to assess moral and ethical dilemmas related to data privacy, cybersecurity, impact of digitalization on identity and social connections, and formulate recommendations on the responsible use of technology.
- Predictive analysis: to assess the potential future directions of the digital body and its impact on society, based on identified technological trends and social changes.

Thus, this study is a theoretical synthesis. Its aim is to develop a holistic view of the digital body in the context of a rapidly changing technological landscape and its impact on humans and society.

RESEARCH RESULTS

As a result of the research, the concept of the digital body as a multi-layered phenomenon was clarified and specified. The phenomenon included not only a set of digital footprints and user profiles, but also a set of biometric data, behavioral patterns, interactive avatars and adaptive interfaces formed under the influence of artificial intelligence and sensory technologies. Analysis of historical development has shown that transformation of human digital presence has gone through several stages: from simple text and graphic representations in early online communities through personalized social profiles to integrated ecosystems where user-related data are continuously collected, processed and used to create dynamic digital representations.

The paper identifies the key functional components of the digital body such as identification (identity and reputation), information and diagnosis (biometrics and health monitoring), interaction (avatars, VR/AR interfaces) and adaptation along with analytics (AI algorithms and personalization mechanisms). It also demonstrates how they are interrelated and influence each other. The study also showed that integration of VR and AR enhances the multidimensionality of the digital body: new forms of physicality and self-representation are created, the boundaries between "real" and "virtual" are blurred, and the experience of identity becomes context-dependent and multiple. An empirical review of the digital body applications in medicine has demonstrated a significant potential of technologies for prevention and individualized treatment: regular monitoring of biometrics and big data analytics make it possible to identify risks in a timely manner, create personalized health plans and improve the effectiveness of clinical decisions.

In education, the results of the study confirmed effectiveness of virtual clinics and simulation platforms for development of clinical thinking and practical skills; VR/AR-based interactive techniques contribute to deep learning of the material and increase the motivation of students. Analysis of socio-cultural effects has shown the dual nature of the digital body effect: on the one hand, technology promotes the expansion of social ties, inclusion and intercultural dialogue; on the other hand, the risks of fragmentation of identity, increased anonymous aggression and possible loss of lively social interaction qualities are noted. The study of legal and technical barriers revealed the main obstacles to the widespread adoption of digital practices such as insufficient infrastructure and digital literacy in individual regions, disparate regulatory approaches and weak protection of user data. Thus, unified standards and enhanced cybersecurity measures must be developed.

The results draw special attention to the impact of AI: it is established that algorithmic personalization and predictive analytics foster convenience and efficiency of digital services, though generating new challenges in the field of privacy, transparency of decision-making and responsibility for automated conclusions. The study assessed the impact of the digital body on the labor market and showed that digitalization and remote work expand employment opportunities and flexibility, but require new competencies and constant retraining; successful professional adaptation is associated with developed technical skills and soft competencies.

The results confirm that the digital body is a dynamic and multifaceted object integrating technological, social, ethical and legal dimensions; it's safe and humanistic development requires interdisciplinary approaches, strengthening digital literacy programs, introducing transparent regulatory mechanisms and improving data protection standards, which will maximize the benefits of technology while minimizing associated risks.

DISCUSSION OF RESULTS

The conducted research, devoted to the concept of the digital body, its historical development, relevance and multifaceted aspects of its impact on modern society, allows us to compare the findings with an extensive body of scientific papers and practical observations. Our results demonstrate that the definition of a digital body as a dynamic virtual representation of a physical body, consisting of anonymous and public data created and controlled by technology, is fully consistent with modern approaches in digital humanities and sociology of technologies. A number of authors also emphasize that this concept is constantly evolving from simple digital avatars to complex digital footprints, covering a wide range of online activity and data collected by Internet of Things devices [22]. The fact is emphasized as advantageous in further movement of mankind towards digitalization and virtualization of many aspects of public life, especially in the field of information systems [23], legal relations between various subjects of law [24], and their legal regulation [25].

Our observations of how virtual reality (VR) and augmented reality (AR) influence the perception of the environment and being, in particular, the shift of the ontological status of "essence" towards multiple realities, are reflected in works analyzing the phenomenology of digital space. Researchers in cyberpsychology and philosophy of technology also note that immersive technologies blur the physical-virtual lines, reshaping self-perception. The examples of VR and AR applications in various fields, from education to entertainment, correlate with the data presented in reports on innovative technologies, where these tools are considered as key drivers of digital transformation.

In healthcare, our conclusions about the growing role of the digital body for medical monitoring, disease prevention, and a personalized treatment approach based on the analysis of big data and biometric information are supported by numerous publications in HealthTech and medical information systems [26]. These studies also point to the significant potential of predictive analytics and machine learning in improving healthcare efficiency, which fully coincides with our conclusions.

Analysis of adaptation to user needs via personalized settings and unique avatars reflects the main trends in the field of human-computer interaction and user experience design. Many works in this field focus on the psychology of personalization, proving that it promotes deep user engagement and formation of their digital identity, which was found in our study as well.

In the context of education, our observations on the introduction of virtual clinics and interactive teaching methods in healthcare and other fields correspond to the trends described in educational research and EdTech publications. The concept of a safe and supportive learning environment for clinical thinking and practical skills is widely supported by leading educational institutions.

Our results regarding social aspects confirm the dual nature of digital technologies: on the one hand, they expand social ties, break down barriers, and foster virtual communities, which

is essential for sociologists and communication specialists. On the other hand, we, like many other researchers in the field of cyberpsychology, note the risks associated with anonymity, fueled online aggression, and potential social isolation. These contradictions are being actively discussed by the scientific community.

The issues of privacy, security of personal data and ethical aspects of digital life identified in our study are universal challenges discussed at the global level. Our conclusions about the growing cyberthreats [27], difficult self-awareness in virtual spaces, and the risk of dependence on technology are consistent with the work of leading experts in cybersecurity, law, and ethics of artificial intelligence [28, 29]. Similar studies emphasize the need for comprehensive legal and technical solutions to protect the rights and well-being of users [30].

Finally, the analysis of the impact Artificial Intelligence (AI) produces on the digital body and transformation of the labor market, including the rise in remote work and the need for new competencies, also correlates with current reports and forecasts on the future of work trends and AI development. Our conclusions about the importance of soft skills, technical skills, and continuous learning are commonly discussed while training specialists for digital economy. Cultural scientists and anthropologists who study the digital transformation of the society confirm that AI influences cultural and social standards as it was found out in our study.

Thus, our research, which covers a wide range of issues from how the digital body is defined to how it impacts work and culture, not only confirms the existing scientific trends, but also contributes to a deeper understanding of the complex human-technology relationship. The general research vectors indicate that the digital body is a central category to study modern reality that requires an interdisciplinary approach and constant reflection on the ethical, social and technical implications of its development.

CONCLUSIONS

The study systematized the concept of the digital body that shows how individuals represent themselves in digital environments, including anonymous, public data, and their collection and management tools (social networks, IoT, mobile applications, cloud services). The historical prerequisites for the formation of the digital body (from the early online profiles of the 1990s to modern platforms), technological components (VR, AR, biometrics, AI), application scenarios (healthcare, education, virtual clinics, remote work, virtual offices) [31] and socio-cultural consequences (changing communication norms, identity issues, cultural integration) have been reviewed [32]. The risks such as privacy, cybersecurity, loss of a sense of real identity, social isolation, technical and regulatory barriers are analyzed separately [33].

The goal has been successfully met in its entirety, as an interdisciplinary image covering key components (technologies, applications, risks and social effects) has been presented.

Recommendations for the development of the field and directions for further research are as follows:

1. Focused empirical research. Use clear methodology to research aspects of the digital body such as the impact of prolonged use of VR/ AR on cognitive and emotional performance; accuracy and reliability of biometric systems under different conditions; the degree of leaks and privacy risks in popular services.
2. Interdisciplinary projects. Make technical specialists, social psychologists, lawyers and ethicists work as a group in order to perform comprehensive assessment of how technologies impact the individual and the community.
3. Long-term longitudinal studies. To track changes in digital identity and psycho-social effects over a long period of time in order to identify cumulative effects and possible adaptive mechanisms.
4. Development and testing of privacy standards and protocols. Research to evaluate the effectiveness of technical and organizational data protection mechanisms (decryption, differential privacy, local data processing, explicit consent management models).
5. Ethical and legal research. Analysis of current regulatory practices, assessment of legislative gaps, and preparation of recommendations on a responsible use of AI, VR/AR, and biometrics.
6. Research on inclusivity and accessibility. Assess technological barriers in different regions and for different demographic groups; develop solutions to reduce digital inequality.
7. Applied pilots in education and medicine. Implement and evaluate pilot projects of virtual clinics and educational programs measuring the effectiveness of training and safety of patients/students.

Possible ways to use the results obtained in further research and practice:

1. Designing secure digital platforms: developers can use conclusions about the risks and needs of users to create more private and manageable digital profiles and avatars.
2. Medical applications: recommendations on the use of biometrics and digital bodies to prevent and monitor diseases can form the basis of remote monitoring protocols and personalized medicine.
3. Educational technologies: the results confirm that virtual clinics and AR/VR simulations are effective learning tools that allow to assess competencies and feedback.
4. Policy and regulation: the collected systematization will allow legislators and regulators to more precisely formulate regulations regarding the storage and processing of personal data, use of AI and protection of user rights.
5. Social interventions: understanding how social isolation and identity shifts impact people is the key to designing effective digital literacy programs that boost mental health and inclusion.
6. Personalization technologies: conclusions made about the importance of adaptation and virtual avatars can be used to create more ethical and user-oriented content and interface personalization systems.

The study confirms that the digital body is a central and multi-layered concept that helps to understand the modern human-tech interaction [34]. Strictly planned empirical research, interdisciplinary collaboration, and development of regulatory and technical tools that guarantee security, privacy, and inclusiveness of digital practices are required to shift from conceptual understanding to practical solutions [35].

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SECURITY OF ELECTRONIC HEALTH RECORDS: FEDERATED BLOCKCHAIN AND POST-QUANTUM CRYPTOGRAPHY

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The article presents a review on the potential of the distributed ledger technology (DLT), particularly federated blockchain, that can be used to create a secure, transparent and patient-managed ecosystem of medical data. The hybrid architecture reviewed uses the blockchain to store immutable metadata and hashes, and manage large amounts of data (for example, diagnostic images) on external cloud storage, which ensures the integrity of data without network overloading. The key aspect of the research is to analyze long-term threats posed by quantum computing that makes current cryptographic standards vulnerable. It is stressed that adoption of post-quantum cryptography (PQC) is required to ensure future security of medical data. An analysis was carried out to compare the leading global (CRYSTALS-Dilithium, Falcon) and Russian (Hypericum, Shipovnik) post-quantum cryptography algorithms.

Keywords: blockchain, post-quantum cryptography, electronic health record, distributed ledger, federated computing, bioethics

Author contribution: Potapov MP — research planning, analysis, editing; Kostrov SA — data collection, analysis and interpretation, preparing a draft manuscript.

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БЕЗОПАСНОСТЬ ЭЛЕКТРОННЫХ МЕДИЦИНСКИХ ЗАПИСЕЙ: ФЕДЕРАТИВНЫЙ БЛОКЧЕЙН И ПОСТКВАНТОВАЯ КРИПТОГРАФИЯ

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Статья посвящена анализу потенциала технологии распределенного реестра, в частности федеративного блокчейна, как основы для создания защищенной, прозрачной и управляемой пациентом экосистемы медицинских данных. Рассмотрена гибридная архитектура, при которой блокчейн используется для хранения неизменяемых метаданных и хешей, а объемные файлы (например, диагностические изображения) размещаются во внешних децентрализованных хранилищах, что гарантирует целостность данных без перегрузки сети. Ключевым аспектом исследования является анализ долгосрочных угроз, связанных с развитием квантовых компьютеров, которые ставят под угрозу существующие криптографические стандарты. Подчеркивается необходимость перехода на постквантовую криптографию для обеспечения будущей безопасности медицинских данных. Проведен сравнительный анализ ведущих мировых (CRYSTALS-Dilithium, Falcon) и перспективных отечественных («Гиперикум», «Шиповник») квантово-устойчивых алгоритмов криптографии.

Ключевые слова: блокчейн, постквантовая криптография, электронная медицинская запись, распределенный реестр, федеративные вычисления, биоэтика

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In the digital age of healthcare, storage and management of electronic health records deserve equal attention both from a technical and bioethical perspective. The issue is pressing due to the exponential growth of healthcare data generated during diagnostics and treatment, including telemedical consultations and wearable technologies. Medical images, genomics and molecular research form the core of them. According to the World Health Organization, healthcare data will reach one-third of global medical data in zettabytes [1]. It increases the risk of leakage and unauthorized access. Thus, in developed countries, healthcare is considered a critical information infrastructure. In 2025, global economic losses from cyber incidents are estimated to reach 10 billion dollars [2, 3].

Patients value not only high-quality and complete healthcare information but also information security, ethical privacy standards, and control over their data. Traditional centralized data storage in medical information systems poses significant risks due to single points of failure.

Blockchain technologies that ensure decentralization, cryptographic protection and flexible safety partly controlled by an individual hold significant promise in line with AI, quantum computations and enhanced cryptography.

The aim of the publication is to introduce the distributed ledger technology used to store health records to the medical community while addressing the issues of enhancing information security and confidentiality through cryptographic algorithms.

MATERIALS AND METHODS

This article articulated an approach for searching in the leading Russian and foreign bibliographic resources such as eLibrary and PubMed, using specialized platforms to analyze scientific

publications including Semantic Scholar, Consensus и Elicit, performing critical analysis, and selecting relevant sources. To be included, publications needed to match the topic of the study, be published between 2018 and 2025, and have both full-text Russian and English versions available. The relevance of sources was initially assessed through abstracts by checking if they focused on the topic of using blockchain technology in the healthcare sector.

A group of experts checked the final manuscript for accuracy. OpenAI ChatGPT-4.1 and Google Gemini 2.5 were used for summarization and grammar correction.

RESULTS AND DISCUSSION

Individuals may erroneously believe that blockchain is a synonym for cryptocurrency though it is just the underlying technology. The technology has made it possible for records to be unchangeable, controllable, accessible and protected no matter if it is used in economics, logistics, management or medicine.

Unlike the traditional centralized systems, which data are controlled by medical institutions, blockchain allows patients to manage their health records with greater autonomy [4].

Users hold a private cryptology key that helps them do the following:

- determine the conditions for data use through smart contracts;
- track all transactions due to blockchain immutability;
- withdraw approvals at any time.

The main property of the blockchain is immutability, as once data are recorded, they cannot be changed or deleted [4].

Blockchains used for storing health records are classified into public, private, and federated (consortium) blockchains based on DLT types. A public blockchain is a decentralized, open network that can be joined by any participant [5]. A private system managed by a single organization is well-suited for tasks that require centralized management and accelerated consensus. On the one part, it can speed up transactions, optimize clinical information flows, and implement policies of access, audit and compliance control at a greater rate. On the other part, private blockchains can suffer from disadvantages such as centralization risks, risks of failure and misuse, and challenges in scaling across institutions and regions [6].

Federated blockchains, also known as consortium or permissioned blockchains, are networks with restricted access, that can be controlled by a predetermined group of participants (medical organizations, laboratories and regulatory bodies), thus maintaining a balance between decentralization and access control. Federated blockchains enable integration of multiple medical institutions into a unified system and provide for the secure exchange of health records.

Also, federated blockchains help process transactions at a higher speed and ensure a greater flow capacity as validating nodes are limited in number and can be controlled. In public networks, the speed is lower as consensus of a greater number of unknown participants is required [5].

Electronic health records can be stored using technological platforms such as Hyperledger Fabric. They combine smart contracts, attribute-based access control (ABAC) and IPFS-based distributed data storage (file system) [7].

In Russia, Masterchain by FinTech Association, the first certified platform, which uses Russian means of cryptographic protection of information, is being actively implemented into the banking sphere. In 2021, Russia launched a blockchain operator for its distributed ledger system. Net processed information is legally significant here. It has been used by the Federal Tax Service of Russia to store computer-readable powers of attorney since 2023 [8].

Public blockchains such as Bitcoin, Ethereum, etc. cannot be directly implemented in healthcare. They are used to store hash functions and references to encrypted data partially solving the issue of confidentiality [7].

Transparency of public blockchains is a valuable advantage for financial and logistic applications. In medicine, however, it is rather a disadvantage. Placing encrypted data on an open network can be considered a form of data leakage because the data, when saved, can be decrypted in future using methods that are currently unavailable [7, 9]. For instance, widely applied ECDSA cryptographic methods based on elliptic curves, which are highly protected in traditional systems, can be broken with Shor's algorithm capable to reclaim the private key using the public key on a quantum computer in polynomial time [10].

A large-scale quantum computer capable of running Shor's algorithm with a sufficient number of qubits (around 2000) and low level of errors will compromise safety mechanisms. Healthcare systems require long-term digital safety. Active scientific and technological developments are transitioning to post-quantum cryptography, key distribution schemes and novel consensus protocols that do not depend on mathematical tasks vulnerable to Shor's algorithms [10].

First and foremost, post-quantum algorithms are based on lattices (lattice-based cryptography), and their security is guaranteed by the difficulty of mathematical problems associated with these lattices (for example, the Shortest Vector Problem (SVP) and the Learning with Errors (LWE) problem), which allow only exponential attacks, even on a quantum computer. Typical algorithms can include as follows [11, 12]:

- NTRUEncrypt is one of the first and most famous systems;
- CRYSTALS-Dilithium is a modern lightweight digital signature scheme recommended by the National Institute of Standards and Technology of the USA (NIST) in 2024 and proposed to replace ECDSA as the main standard. It demonstrates an optimal balance between the speed of key generation, signing, verification, and keys and signatures of "moderate" size [12];
- Falcon is recommended by NIST as an additional signature scheme for special cases where maximum compactness of signatures and keys is desired, as well as for applications that prioritize high signature verification speed [11].

In addition to lattice cryptography, solutions based on isogeny-based cryptography and the morphism of a path between two different elliptic curves, are of particular interest. SIKE (Supersingular Isogeny Key Encapsulation) was a well-known post-quantum cryptography algorithm based on isogenies, which also participated in the post-quantum standardization competition announced by NIST. However, the algorithm was cracked in 2022. Currently, other algorithms (SQISign — Short Quaternion and Isogeny Signature, CSIDH — Commutative Supersingular Isogeny Diffie-Hellman, etc.) are at the level of academic research and cannot be widely applied in practice [13].

Kyber is an advanced post-quantum encryption algorithm selected by the US National Institute of Standards and Technology (NIST) as the main standard for key encapsulation (KEM) mechanisms in the era of quantum computing [12].

Unfortunately, domestic developments are still significantly behind world standards. National standard systems, including GOST 34.10-2012 and GOST 34.10-2018, are also based on elliptic curve operations and are vulnerable to quantum

Table. Comparison of post-quantum cryptographic algorithms

Specification	Hypericum	Shipovnik	Falcon	CRYSTALS-Dilithium
Developer	QApp (Russia)	Kryptonite (Russia)	International group	International group
Cryptographic basis	Hash functions (SPHINCS+)	Coding theory (Stern based protocol)	NTRU grids	Grids (LWE)
Computed task	Hash functions Streebog GOST	Decoding an accidental linear code	Searching for short vectors in NTRU-grid	Ring learning with errors
Public key (bytes)	64	512	897 (Falcon-512) 1793 (Falcon-1024)	1,312 (Dilithium2) 1,952 (Dilithium3) 2,592 (Dilithium5)
Signature size (bytes)	18,292–58,460	~ 600,000	752 (Falcon-512) 1462 (Falcon-1024)	2,420 (Dilithium2) 3,293 (Dilithium3) 4,595 (Dilithium5)
Performance	Relatively slow signature and verification	Rapid generation of keys and signature verification	Slow generation of keys with rapid verification of signature	Rapid generation of keys and signature verification
Patterns	Very large size of signature, slow functioning	Long process of signature creation	Most compact signatures, high productivity and difficult implementation	Balanced features, simple implementation, good productivity

cryptanalysis. Academic research and development of domestic post-quantum algorithms are still underway [14–17]:

Hypericum is an algorithm of digital signature developed by QApp in line with Technical Committee 26 of Rosstandard. To implement SPHINCS+ postquantum digital signature scheme, the works on using the Russian standardized Streebog hash function are in progress [17].

Shipovnik is an algorithm developed by Kryptonite, which is based on the complex task of an accidental linear code decoding. At present, effective algorithms that allow standard or quantum computers to solve some types of problems are unknown. In theory, they cannot be created even using computers of tomorrow with millions operating qubits. However, a large signature size is impractical for blockchain use.

The Oblepikha algorithm presented during the RusCrypto'2025 conference is also of interest. It is based on the theory of grids (LIP task) and uses the decreasing signature size while preserving a high level of stability.

Hypericum and Shipovnik can be classified as future state cryptographic standards in Russia with open implementations in the C language, including many hosted on GitHub: https://github.com/QAPP-tech/shipovnik_tc26 and https://github.com/QAPP-tech/hypericum_tc26 (table).

Apart from encryption, permissioned systems used in healthcare enable flexible access control. Hybrid models that combine role-based and attributive-based access controls (RBAC and ABAC) and multitiered systems of access control are used in practice.

Role-based access control (RBAC) is used by patients to assign various roles (doctor, nurse, researcher) with respective access levels [18].

Attribute-based access control (ABAC) enables to create more flexible access policies based on numerous attributes such as time frames, geographic location, data types and purpose of use.

Technological solutions are based on multitiered architectures where a user interface intuitively integrates management of approvals and review of medical data. The level of smart contracts provides a seamless way to execute business logic including issue, change and withdrawal of consents, as well as monitoring of all operations.

Every transaction such as appointment entry, prescriptions, test results, medical reports and discharge summaries can be recorded within the chain of blocks creating an indisputable and chronologically adjusted audit trail. However, blockchains cannot store large files. Attempts to include diagnostic images (MRI scans, CT scans, etc.) or other large data in the blockchain will result in an exponential growth of registry size, decrease of network productivity and unreasonably high transaction expenses [19].

In a typical blockchain scenario, blockchain uses hashes and meta-data that make transactions immutable and transparent, whereas large medical files are placed in decentralized file systems (IPFS). It warrants that the data are highly accessible and integral. If a file in a blockchain-based repository is altered even by a single byte, its cryptographic hash will change, which will break the link to subsequent blocks in the chain, immediately revealing the tampering to anyone inspecting the ledger [5, 19].

The public key of a patient functions both as an address or network ID that can be freely shareable with others (medical institutions or insurance companies) to obtain access to the data. However, any transaction, including approval for review or change in health records, should be signed using a respective private key [18].

Despite the advantages, the system makes a patient liable. The loss of a private key is critical. In totally decentralized (public) blockchain systems, such a loss means a complete and permanent loss of access to medical health records and their control. The protocols restoring personalities and keys can be implemented in the federative blockchain. A consortium can act as a trusted arbiter. Thus, if patients lose the key, their personality can be verified and a new key can be provided to access the records. It is common to use multi-signature schemes when signatures of several parties are required to restore the access.

Digital literacy should be continuously improved, as many doctors and patients can't manage keys effectively and are still unaware of how blockchain works. Low awareness leads to digital inequality and makes new solutions less available for individuals, countries and regions.

CONCLUSIONS

A distributed ledger technology, particularly federated blockchain (consortium), represents a perspective solution that can dramatically increase the level of data protection, ensure their integrity and allow patients to control their data. A balance between a complete decentralization of public networks and centralized control of public systems is required. Managing the consortium of authorized members (medical organizations, laboratories, insurance companies, state regulators) corresponds to the structure of healthcare system and enables high speed of transactions and flow capacity. Hybrid storage in decentralized file-based systems and use of blockchain to store hashes and metadata ensure integrity without overloading the network.

Russian developments such as the Masterchain platform have already displayed the technology potential, its legal significance in the banking sphere and perspectives of use in healthcare and adjacent fields.

The existing cryptographic standards including GOST are vulnerable to quantum cryptoanalysis. Thus, shifting to post-quantum cryptography is both a key perspective and a challenge. To create truly protected medical systems of the future, quantum-resistant algorithms, such as globally used CRYSTALS-Dilithium and Falcon, and Russian-based Hypericum and Shipovnik, should be developed and standardized. A wide-ranging application requires improved legislation in the field of data protection, updated GOSTs, and certification of cryptographic data protection tools.

Successful implementation of the technologies depends on how technical, social and organizational tasks can be solved, primarily on improved digital literacy of physicians and patients. Blockchain advantages cannot be implemented completely and digital risks are impossible to avoid when the principles of blockchain operation and responsible management of cryptographic keys are failed to be understood.

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ETHICAL AND CLINICAL DILEMMAS OF USING LIPID-LOWERING THERAPY IN CHILDREN WITH HEREDITARY DYSLIPIDEMIA

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The article reviews the bioethical concern in providing lipid-lowering therapy to children with hereditary dyslipidemia. The concern is associated with the gap between clinical recommendations and official prescribing information. The purpose of the research was to perform a comparative analysis of regulatory documents, clinical recommendations and prescribing information of 11 medicinal preparations including statins, cholesterol absorption inhibitors, fibrates, omega-3 polyunsaturated fatty acids and PCSK9 inhibitors. The analysis has shown the lack of pediatric-specific data regarding effectiveness and safety of 45% prescribed medications. It imposes direct age restrictions and prevents their use in patients under 18. At the same time, clinical guidelines advocate for early initiation of therapy to reduce the lifetime risk of cardiovascular complications in children with familial hypercholesterolemia. The discovered regulatory inconsistency creates a legal barrier and makes physicians encounter ethical difficulties. The results emphasize the need to update regulatory documents and conduct additional clinical studies to ensure a safe use of lipid-lowering drugs in pediatric practice.

Keywords: familial hypercholesterolemia, pediatrics, cardiology, lipid-lowering therapy

Author contribution: the authors contributed equally to the work.

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ЭТИЧЕСКИЕ И КЛИНИЧЕСКИЕ ДИЛЕММЫ ГИПОЛИПИДЕМИЧЕСКОЙ ТЕРАПИИ ПРИ НАСЛЕДСТВЕННЫХ ДИСЛИПИДЕМИЯХ У ДЕТЕЙ

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В статье рассмотрена биоэтическая проблема назначений гиполипидемической терапии детям с наследственными дислипидемиями, связанная с разрывом между клиническими рекомендациями и официальными инструкциями лекарственных средств. Целью исследования был сравнительный анализ нормативно-правовых документов, клинических рекомендаций и инструкций по применению 11 препаратов, включая статины, ингибиторы абсорбции холестерина, фибраты, омега-3-полиненасыщенные жирные кислоты и ингибиторы PCSK9. Анализ показал, что у 45% препаратов официально отсутствуют данные о безопасности и эффективности в педиатрии, что накладывает прямые возрастные ограничения и препятствует их применению у пациентов до 18 лет. В то же время клинические рекомендации настаивают на раннем начале терапии для снижения пожизненного риска кардиоваскулярных осложнений у детей с семейной гиперхолестеринемией. Обнаруженное нормативное несоответствие создает правовой барьер и ставит врачей в этически сложное положение. Результаты подчеркивают необходимость обновления регуляторных документов и проведения дополнительных клинических исследований для обоснования безопасного применения гиполипидемических средств в детской практике.

Ключевые слова: семейная гиперхолестеринемия, педиатрия, кардиология, гиполипидемическая терапия

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Initiating lipid-lowering therapy in children with hereditary dyslipidemia presents a complex bioethical dilemma that operates at the intersection of the recommendations and regulatory prescriptions. Clinical recommendations based on long-term cardiovascular risks state that some lipid-lowering drugs should already be used in childhood. However, the official contraindications listed in the instructions of many drugs hinder the use of most statins in pediatric practice (with rare exceptions). Thus, a physician has to make a difficult choice by either following the approved instructions or considering the treatment that goes beyond them. This article is devoted to the bioethical analysis of this conflict.

MATERIALS AND METHODS

During the present study, a systematic comparative analysis of regulatory and clinical databases regulating the use of lipid-lowering therapy in pediatric practice was carried out. Special emphasis was made on finding and analyzing the contradictions between official patient information leaflets and updated clinical guidelines.

Preparations for analysis were selected based on their mentioning in modern clinical recommendations to treat inherited dyslipidemia in children, in particular homozygous and heterozygous familial hypercholesterolemia. The final sample included 11 medicinal preparations belonging to basic pharmacological groups such as statins (atorvastatin, rosuvastatin, pitavastatin, simvastatin), cholesterol absorption inhibitors (ezetimibe), fibrates (fenofibrate), omega 3 fatty acids, PCSK9 inhibitors (alirocumab, evolocumab) and inclisiran.

An official patient information leaflet registered in the Russian Federation was analyzed for every medicinal preparation. Regulatory guidance was examined as of August 2025 through official sources such as the State Register of

Medicines and Information Resources of Manufacturers of Pharmaceutical Products. When analyzing the instructions, the Contraindications and Pediatric Use subsections were given special attention. Wording about age restrictions, specific age thresholds, and justifications for the restrictions were of particular interest. The obtained data were included within a single base with a subsequent comparative analysis.

Relevant clinical recommendations were studied simultaneously. Differences in approaches to the age of initiating therapy, selection of first-line drugs and dosage schedules in pediatric practice were compared.

RESEARCH RESULTS

A bioethical contradiction occurring during selection of therapy for children with hereditary dyslipidemias, in particular familial hypercholesterolemia, was detected during the research. The contradiction consists in the gap between pressing clinical recommendations [1] and officially registered patient information leaflets [2–12] for the reviewed medicinal preparations.

The research is relevant due to high epidemiologic prevalence of inherited dyslipidemias. Heterozygous familial hypercholesterolemia (HeFH) is a moderately common genetic disease, which is present in 1 per 200–250 of the European population. Homozygous familial hypercholesterolemia (HoFH) is a rare genetic condition with an estimated frequency of 1 in 160,000 to 1 in 300,000, which is characterized by an extremely unfavorable outcome and early cardiovascular complications. The combination of the high population prevalence of heterozygous FH and the exceptional severity of homozygous FH shows the medical and social significance of the problem and the need to develop clear algorithms for managing pediatric patients, including early diagnosis and timely initiation of therapy [13].

Clinical recommendations based on data from numerous long-term studies and meta-analyses clearly demonstrate the need for early initiation of drug therapy to reduce lifelong cardiovascular risk. The use of lipid-lowering drugs is considered as a treatment strategy aimed at preventing early atherosclerosis and its complications.

Meanwhile, most official prescribing instructions contain direct age restrictions or lack data on the use of the medicinal agents in pediatric practice. This is how legal and regulatory concerns for physicians arise [14].

To provide for a detailed analysis of this conflict, a list of drugs mentioned in the current clinical guidelines for treatment of homozygous and heterozygous FH in children has been compiled:

- statins: atorvastatin, rosuvastatin, pitavastatin, simvastatin;
- cholesterol absorption inhibitors: ezetimibe;
- PCSK9 inhibitors: alirocumab, evolocumab;
- other lipid-lowering agents: bempedoic acid, omega-3 polyunsaturated fatty acids, fibrates, inclisiran

The results of the comparative analysis demonstrate a pronounced regulatory gap.

Analysis of basic prescribing information has shown as follows:

- five of the eleven drugs reviewed have formal age-related restrictions for pediatric patients. In the Contraindications or Pediatric Use sections it has been shown that safety and effectiveness of rosuvastatin, bempedoic acid, inclisiran, fenofibrate and omega 3 fatty acids are not established in children from 0 to 18 years old, whereas data on their use are limited [2–6]. The wording officially prohibits their use in minor children due to the lack of sufficient evidential base required to register the respective indications;
- four medicinal agents such as ezetimibe, evolocumab, simvastatin and atorvastatin are officially approved in children 10 years and older [7–10];
- alirocumab is contraindicated in children under 8, due to the lack of safety and effectiveness data for this age [11];
- pitavastatin is associated with the following age restrictions: it is contraindicated in children under 6 due to the lack of sufficient data for patients of this age [12].

Thus, a considerable part of medicinal agents registered in the Russian Federation have direct age-related limitations in patient information leaflets or lack sufficient clinical data hindering their use in pediatric practice. It forms a significant legal and regulatory barrier for a treating physician. According to par. 4 of article 37 of Federal Law dated November 21, 2011 No. 323-ФЗ (amended as of December 28, 2024) ‘On fundamental healthcare principles in the Russian Federation’ [14], medicinal agents should be prescribed and used based on the patient information leaflet only. Thus, a direct age-related limitation (‘contraindicated to children under 18’) or information on the lack of using the prescription drugs in pediatric populations makes legal prescription of the medicinal agent to pediatric population impossible thus creating a legal dilemma for a clinician when the medicinal agent is essential for therapeutic treatment.

CONCLUSIONS

The conducted research resulted in detection of a bioethical and regulatory contradiction associated with the use of lipid-lowering therapy among children with inherited dyslipidemias. The purpose of the study to detect and analyze a discrepancy between clinical recommendations and patient information leaflets has been achieved. According to the analysis, modern clinical practice recommends early initiation of therapy so that a long-term cardiovascular risk could be decreased, whereas patient information leaflets contain significant age-related restrictions and shortage of data that hinder the use of certain lipid-lowering agents in childhood.

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THE STUDY OF RELATIVE BIOAVAILABILITY OF OCULAR SUSPENSION OF 4-(5-METHYL-1,3,4-OXADIAZOLE-2-YL)-BENZENESULFONAMIDE IN RABBITS

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4-(5-methyl-1,3,4-oxadiazole-2-yl)-benzenesulfonamide (ODASA), which is a novel selective type II carbonic anhydrase inhibitor for treating open-angle glaucoma, is undergoing preclinical testing. Pharmacokinetics of the substance have only been studied in rats. Prior to clinical studies, it is necessary to assess the systemic exposure of ODASA in non-rodents. ODASA was administered to Soviet Chinchilla rabbits at a dose of 0.28 mg/kg. About 40 µl of ocular suspension of ODASA was instilled into each eye of animals from the first group, whereas the second group received intraperitoneal injections of the investigational drug. Each group consisted of 6 male rabbits. Samples were obtained prior to administration of ODASA and during 288 hours following the administration at 16 time points. A 10% ascorbic acid solution was added to plasma before freezing. The samples were analyzed using HPLC-MS/MS. Following eyedrop instillation, relative bioavailability for ODASA was 31% as compared to IP administration. Thus, as ODASA was well absorbed into the systemic circulation of rabbits following topical eyedrop instillation, testing its pharmacokinetics in healthy volunteers will be obligatory if the preparation proceeds to phase 1 of clinical studies.

Keywords: selective carbonic anhydrase inhibitor, pharmacokinetics, bioavailability, rabbit, plasma, open-angle glaucoma

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Author contribution: Yaichkov II — experimental design development, analysis of rabbit plasma samples, performing statistical calculations, writing an article; Volkhin NN, Petukhov SS, Lazaryants OE — conducting the experiments on rabbits.

Compliance with ethical standards: the study was conducted in compliance with all ethical standards recommended in the Russian Federation. Rabbits were selected to evaluate the pharmacokinetic parameters and relative bioavailability of ODASA as other non-rodent species. The animals were kept in individual cages of a sufficient size. Access to water and mixed feed was available free-choice, except for 4 hours before administration and 2 hours after administration of the investigational preparation. The animals were housed at room temperatures of 20 °C, humidity of 40–65%, and a 12/12 h light–dark cycle. The experimental animals were under the supervision of a veterinarian throughout the experiment. Each group had a minimum allowable sample size for pharmacokinetic studies in the Russian Federation. This study was approved by the Independent Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education Yaroslavl State Medical University of the Ministry of Health of the Russian Federation, Protocol No. 2 dated 04/20/2025.

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ИЗУЧЕНИЕ ОТНОСИТЕЛЬНОЙ БИОДОСТУПНОСТИ ГЛАЗНОЙ СУСПЕНЗИИ 4-(5-МЕТИЛ-1,3,4-ОКСАДИАЗОЛ-2-ИЛ)-БЕНЗОЛСУЛЬФОНАМИДА НА КРОЛИКАХ

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Новый селективный ингибитор карбоангидразы II типа 4-(5-метил-1,3,4-оксадиазол-2-ил)-бензолсульфонамид (ODASA) для лечения открытоугольной глаукомы проходит доклинические испытания. В настоящий момент его фармакокинетика изучена только на крысах. Перед началом клинических исследований ODASA необходимо оценить его системную экспозицию на втором виде животных, который не относится к грызунам. ODASA вводили кроликам породы «Советская Шиншила» в дозе 0,28 мг/кг. Первой группе проводили инстилляцию глазной суспензии в каждый глаз в объеме около 40 мкл, второй группе — ее внутрибрюшинное введение. В состав каждой группы входило по 6 особей мужского пола. Образцы крови отбирались до введения ODASA, а также на протяжении 288 ч после его введения в 16 временных точках. До заморозки к полученной плазме добавлялся 10% раствор аскорбиновой кислоты. Анализ образцов проводили методом ВЭЖХ-МС/МС. Величина относительной биодоступности действующего вещества после глазной инстилляции по сравнению с внутрибрюшинной инъекцией составила около 31%. Таким образом, из-за всасывания ODASA в системный кровоток при местном применении у крыс и у кроликов в случае проведения первой фазы клинических испытаний обязательно изучение его фармакокинетики на здоровых добровольцах.

Ключевые слова: селективный ингибитор карбоангидразы, фармакокинетика, биодоступность, кролик, плазма, открытоугольная глаукома

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Соблюдение этических стандартов: исследование выполнено с соблюдением всех этических стандартов, рекомендованных в Российской Федерации. Кролики были выбраны для оценки фармакокинетических параметров и относительной биодоступности ODASA в качестве второго вида, который не относится к грызунам. Животные содержались в индивидуальных клетках достаточной площади. Доступ к воде и комбикорму ограничивался за 4 часа до и 2 часа после введения изучаемого препарата. На протяжении оставшейся части эксперимента питье и питание были свободными. В виварии был 12-часовой цикл смены освещения, температура — 20–25 °C и влажность — 40–65%. Подопытные животные на протяжении всего эксперимента находились под наблюдением ветеринара. Объем выборки в каждой исследуемой группе был минимально

допустимым согласно требованиям к проведению фармакокинетических исследований, рекомендованных в Российской Федерации. Данное исследование получило одобрение независимого этического комитета Федерального государственного бюджетного образовательного учреждения высшего образования «Ярославский государственный медицинский университет» Министерства здравоохранения Российской Федерации, протокол от 20.04.2025 № 2.

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Novel selective type II carbonic anhydrase inhibitor 4-(5-methyl-1,3,4-oxadiazole-2-yl)-benzenesulfonamide (ODASA) (Fig. 1A) is a promising new molecule for treating open-angle glaucoma. The compound is undergoing preclinical testing. It has been shown to lower intraocular pressure after topical ocular dosing. ODASA reduces the risk of any systemic adverse drug reactions. Its effect can last up to 24 hours [1]. 1% ophthalmic suspension of ODASA has been currently engineered. In rats, relative bioavailability (RB) is over 80% when the preparation is instilled in the eye compared to an intraperitoneal administration. ODASA enters the systemic circulation and is then hydroxylated. The main reaction involves the methyl group on the 1,3,4-oxadiazole ring, leading to the formation of 4-[5-(hydroxymethyl)-1, 4-oxadiazole-2-yl]-benzenesulfonamide (M1) (Fig. 1B). The minor reaction affects the sulfonamide group, forming the metabolite N-hydroxy-4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide (M2) (Fig. 1C) [2].

According to regulatory requirements, the study of pharmacokinetics and bioavailability should be conducted in two species (one non-rodent) [3]. In this case, rabbits are commonly used. They are the most affordable lab animal species [4–7]. Beagle dogs [8–9], minipigs [10–11], and monkeys [12–14] are less frequently used as a second species. ODASA shows limited solubility in water, which makes its intravenous administration difficult and study of absolute bioavailability impossible. Thus, RB is calculated following intraperitoneal injection.

High-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) is the most common method for analyzing biological samples in pharmacokinetic studies. An express method has been developed for quantitative determination of ODASA and its hydroxylated derivatives in laboratory animal blood plasma. Protein precipitation was used to prepare samples. The minor metabolite N-hydroxy-4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide is chemically unstable in biological objects. Therefore, stabilization with a 10% ascorbic acid solution is necessary after plasma sampling [2].

Thus, the work is aimed at calculation of pharmacokinetic parameters and relative bioavailability of ocular suspension of 4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide in rabbits by analyzing samples with HPLC-MS/MS.

MATERIALS AND METHODS

The study was conducted using 3–4-month-old Soviet Chinchilla male rabbits obtained from the SMK Stezar nursery. It was a parallel group study investigating RB. The design was used because of deposition of ODASA within erythrocytes and its long half-life [2]. According to the ethical principles, the sample

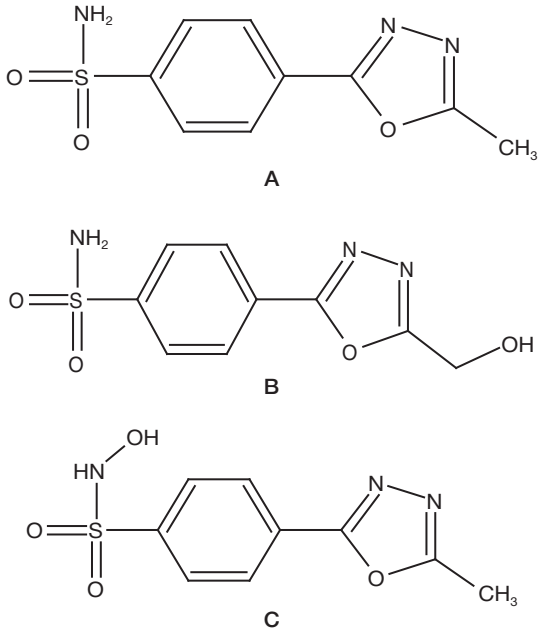


Fig. 1. Structures of 4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide and its metabolites 4-[5-(hydroxymethyl)-1,3,4-oxadiazol-2-yl]-benzenesulfonamide (B) and N-hydroxy-4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide (C)

size was minimally allowable for pharmacokinetic studies [3, 15]. A vivarium housed animals in comfortable conditions using individual cages. Access to water and mixed feed was available free-choice, except for 4 hours before administration and 2 hours after administration of the investigational preparation. Blood sampling from the lab animals was quick and relatively painless. Thus, no anesthesia was used. This study was approved by the Independent Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education Yaroslavl State Medical University of the Ministry of Health of the Russian Federation, Protocol No. 2 dated 04/20/2025.

About 40 µl of 1% ocular suspension of ODASA was instilled into each eye (EI) of animals from the first group, including 6 rabbits weighing 2.84 ± 0.05 kg (M± SEM). It corresponded to a dose of 0.28 mg/kg. 6 other animals with a weight of 3.13 ± 0.05 kg (M±SEM) received an equivalent dose of intraperitoneal (IP) injections of the investigational drug. A 0.2 mL blood sample was drawn from a vein using an insulin syringe as in other similar studies [4–6]. Samples were obtained prior to administration of ODASA and at 30 min, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, 192 hours, 240 hours, and 288 hours following the administration. K_3EDTA was chosen as an anticoagulant. The plasma obtained after centrifugation was stabilized with a 10% ascorbic acid solution in a 1:2 volume ratio (ascorbic acid solution: plasma). The samples were stored at or below — 70 °C till analysis.

A validated bioanalytical technique was used to quantitatively measure the concentration of ODASA and its metabolites. The solution of methanol containing 4-(3-methyl-6-oxo-5,6-dihydropyridazine-1(4H)-yl)-benzenesulfonamide, an internal standard, was added to precipitate the proteins and prepare the samples. To do that, a 100 µl reagent was combined with 20 µl of stabilized plasma. The mixture was stirred and centrifuged for 5 min at 10,000 rpm. The supernatant was transferred to micro-inserts and analyzed. A HPLC-MS/MS system was used, including Agilent 1260 Infinity chromatograph (Germany) and AB Sciex QTRAP5500 mass spectrometer (Singapore). Kinetex Phenyl-Hexyl column (50*4.6 mm, 2.6 microns) and Phenyl SecurityGuard Ultra Catridge pre-column (4.6 mm, 2.6 microns) were used for chromatographic separation. The Multiple Reaction Monitoring (MRM) mode was employed to detect the analytes and the internal standard [2]. The analytical range of plasma concentrations measured was 2–2000 ng/ml for ODASA and M1, and 0.5–500.0 ng/ml for M2.

Non-compartmental analysis was used to determine the pharmacokinetic parameters. Maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), the area under the pharmacokinetic curve capturing drug exposure from time zero to the last measurable concentration (AUC_{0-t}), the area under the curve from zero to infinity ($AUC_{0-\infty}$), half-life ($T_{1/2}$), mean residence time (MRT), apparent volume of distribution (Vd/F), and apparent clearance (Cl/F) were calculated for ODASA and its metabolites using R v. 3.3.2 (Bear v. 2.7.7) package software.

The rate of conversion (R(M)) of the active substance into a metabolite was calculated using the formula:

$$R(M)=\frac{AUC_{0-\infty}\ (M)}{AUC_{0-\infty}\ (ЛС)}\times 100\%,$$

where $AUC_{0-\infty}$ (M) is $AUC_{0-\infty}$ of plasma metabolite;
$AUC_{0-\infty}$ (Drug) is $AUC_{0-\infty}$ of ODASA.

THE RESULTS OF THE STUDY AND THEIR DISCUSSION

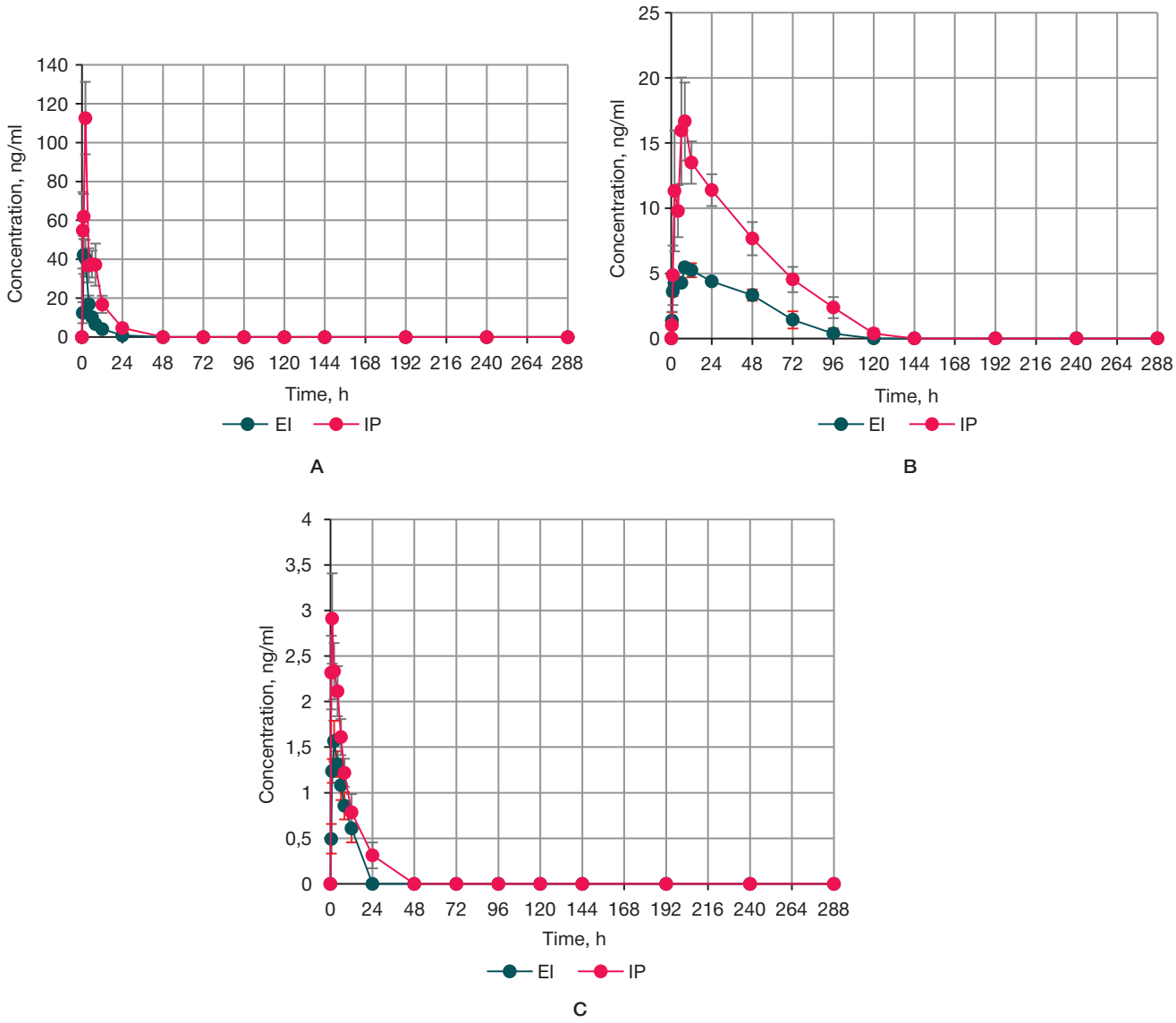
ODASA peak plasma concentration was 58.6 ± 7.2 ng / ml (M ± SEM) within 1 h after therapeutic administration (table). After 48 hours, the content of the active substance in this biological fluid was below the lower limit of quantitation (LLOQ) (Fig. 2A). Following eyedrop instillation, RB for ODASA was 30.76% as compared to IP administration, which is 2.5-fold lower than that in rats. In both modes of administration, the half-life of ODASA was over 6 times shorter than that in rats [2].

Following eyedrop instillation, T_{max} of main metabolite M1 occurred later than that of ODASA and M2. It was detected in plasma over the time range from 0 to 120 hours (Fig. 2B). Its $T_{1/2}$ was about 1.5 times shorter than in rats [2]. The peak concentration of the N-hydroxy derivative was reached from

Table. Pharmacokinetic parameters of 4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide and its metabolites in rabbit plasma

Preparation		ODASA (*n* = 6)		M1 (*n* = 6)		M2 (*n* = 6)	
Mode of administration		EI	IP	EI	IP	EI	IP
C_{max}, ng/ml	M ± SEM	58.6 ± 7.2	129.8 ± 11.4	5.9 ± 0.4	21.59 ± 2.73	1.66 ± 0.20	3.37 ± 0.4
$T_{max,\ h}$	Median (min.-max)	1.0 (1.0–2.0)	2(0.5–2.0)	8 (8–12)	7.0 (2.0–12.0)	1.5 (1.0–2.0)	1.0 (0.5–2.0)
$AUC_{0-t,}$ ng*h/ml	M ± SEM	188 ± 19	611 ± 91	256 ± 41	744 ± 73	11.9 ± 1.6	24.4 ± 4.7
$AUC_{0-\infty,}$ ng*h/ml	M ± SEM	210 ± 22	670 ± 100	430 ± 47	904 ± 100	21.5 ± 3.2	32.6 ± 6.4
$T_{1/2,}$ h	M ± SEM	5.2 ± 1.1	5.7 ± 1.1	48.2 ± 4.2	33.6 ± 5.0	9.4 ± 1.7	9.2 ± 1.9
MRT, h	M ± SEM	4.8 ± 0.8	6.2 ± 0.9	28.9 ± 3.4	34.9 ± 4.7	5.2 ± 0.3	6.6 ± 1.0
Cl/F, ml/h	M ± SEM	498.4 ± 46.4	169.8 ± 28.3	245.7 ± 24.9	120.6 ± 18.5	5141 ± 682	3816 ± 788
Vd/F, ml/kg	M ± SEM	3664 ± 733	1418 ± 429	16730 ± 1686	5276 ± 510	64388 ± 7033	40855 ± 2969
R(M)	M ± SEM	–	–	2.122±0.292	1.513±0.301	0.106±0.017	0.050±0.008

Note: ODASA — 4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide; M1 — 4-[5-(hydroxymethyl)-1,3,4-oxadiazol-2-yl]-benzenesulfonamide; M2 — N-hydroxy-4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide; EI — eyedrop instillation; IP — intraperitoneal administration.



Note: EI— eyedrop instillation; IP — intraperitoneal administration.

Fig. 2. Pharmacokinetic profiles of 4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide (A) and its metabolites 4-[5-(hydroxymethyl)-1,3,4-oxadiazol-2-yl]-benzenesulfonamide (B) and N-hydroxy-4-(5-methyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide (B) in rabbit plasma (error intervals: ± SEM)

1 hour to 2 hours after instillation, just like in the case of the active substance (Fig. 2C). Following eyedrop instillation, $T_{1/2}$ of M2 was about 10 hours. It is approximately 3 times shorter than in rats [2]. The compound concentrations in plasma samples were lower than the LLOQ at 24 hours following instillation in the eye and at 48 hours following intraperitoneal administration.

In experiments with rabbits, ODASA and its metabolites had high apparent volume of distribution (table). They were significantly higher than the actual volume of circulating blood. It means that the investigational agents penetrate well into the organs and tissues of animals.

While using the therapeutic method of administration, the rate of conversion of ODASA to M1 was 2.122 ± 0.292, whereas the rate of conversion of ODASA to M2 was 0.106 ± 0.017 (M ± SEM). This is approximately 10 times higher than the values of R(M) of these hydroxylation products of the active substance calculated in rats. The difference can be explained by a lower preparation dose per unit of body weight and lower plasma concentrations of ODASA. The active centers of microsomal enzymes were less saturated, and ODASA biotransformation occurred much faster. For this reason, clearance values of ODASA in rabbits after EI are over 40 times higher than in rats [2].

Thus, ODASA was well absorbed into the systemic circulation of rabbits following topical eyedrop instillation. High relative bioavailability of the active agent was also detected in the pharmacokinetic study in rats. If the preparation proceeds to phase 1 of clinical studies, testing its pharmacokinetics in healthy volunteers will be obligatory.

CONCLUSIONS

1. ODASA can enter the systemic circulation of rabbits if instilled into the eyes.
2. Relative bioavailability of ODASA after instillation into the eyes was 30.76% compared with intraperitoneal administration.
3. The rate at which ODASA and its metabolites are eliminated differs across species. It is faster in rabbits than in rats.
4. As ODASA is absorbed after topical application in animals, the list of phase I clinical trials should include the study of pharmacokinetics.

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METHODS FOR THE DETECTION OF ETHYLENE GLYCOL AND DIETHYLENE GLYCOL IN MEDICINAL PREPARATIONS: RELEVANCE, CLASSICAL AND PROMISING SCREENING APPROACHES

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This review summarizes and analyses methods for controlling ethylene glycol (EG) and diethylene glycol (DEG) impurities in pharmaceutical products. Contamination of medicinal products with these substances threatens the safety of patients, which is confirmed by numerous mass poisoning incidents throughout history and in modern times. The main reason is using toxic glycols instead of safe fillers such as propylene glycol and glycerol. The article presents systematic review of modern EG and DEG determining methods that range from standard pharmacopoeia methods to perspective screening tools. Particular attention is given to the relevance of development and implementation of prompt, precise and affordable screening solutions to be used at all stages of the pharmaceutical supply chain. The World Health Organization (WHO) Initiatives, including the target product profile (TPP), which aims to enforce these solutions, have been reviewed. It is emphasized that shifting from traditional centralized laboratory testing to decentralized methods is essential to prevent falsification and ensure safety of patients.

Keywords: ethylene glycol, diethylene glycol, pharmacopoeia analysis, chromatography, drug adulteration, pharmaceutical safety, screening methods, World Health Organization (WHO)

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МЕТОДЫ ОБНАРУЖЕНИЯ ЭТИЛЕНГЛИКОЛЯ И ДИЭТИЛЕНГЛИКОЛЯ В ЛЕКАРСТВЕННЫХ ПРЕПАРАТАХ: АКТУАЛЬНОСТЬ, КЛАССИЧЕСКИЕ И ПЕРСПЕКТИВНЫЕ СКРИНИНГОВЫЕ ПОДХОДЫ

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В данном обзоре систематизированы и проанализированы методы контроля токсичных примесей этиленгликоля (ЭГ) и диэтиленгликоля (ДЭГ) в фармацевтической продукции. Проблема загрязнения лекарственных средств данными веществами представляет собой глобальную угрозу безопасности пациентов, что подтверждается многочисленными историческими и современными случаями массовых отравлений. Основной причиной является использование токсичных гликолей вместо безопасных наполнителей, таких как пропиленгликоль или глицерин. В статье представлен систематический обзор современных методов определения ДЭГ и ЭГ — от стандартных фармакопейных до перспективных скрининговых технологий. Особое внимание уделено актуальности разработки и внедрения быстрых, точных и экономически доступных скрининговых решений для применения на всех этапах фармацевтической цепочки поставок. Рассмотрены инициативы Всемирной организации здравоохранения, в том числе проект целевых профилей продукции (ЦПП), направленные на стимулирование создания таких решений. Подчеркнута важность перехода от централизованной лабораторной диагностики к децентрализованным технологиям для предотвращения фальсификаций и обеспечения безопасности пациентов.

Ключевые слова: этиленгликоль, диэтиленгликоль, фармакопейный анализ, хроматография, фальсификация лекарственных средств, фармацевтическая безопасность, скрининговые методы, Всемирная организация здравоохранения (ВОЗ)

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The purity of pharmaceuticals and finished products is crucial for modern medicine. Even trace amounts of highly toxic impurities in medications can be dangerous because they can reduce therapeutic effectiveness and cause serious health problems. Ethylene glycol (EG) and diethylene glycol (DEG) impurities are toxic contaminants that enter medicinal preparations and liquid oral medicines, like syrups and suspensions in particular, through poor quality and falsified excipients such as glycerol, propylene glycol, polyethylene glycol and sorbitol [1, 2]. (A more detailed description of risks for every substance is provided in Exhibit).

The toxicological danger of EG and DEG stems from different metabolic pathways. EG and DEG are converted by the alcohol dehydrogenase to glycolic and glyoxylic acids

(for EG) and 2-hydroxyethoxy acetic acid (for DEG). These metabolites cause severe metabolic acidosis, crystalluria, and direct nephrotoxic effects, leading to acute tubular necrotization and, as a result, acute renal failure with a high mortality rate, especially among children [3, 4].

Not only theoretical assumptions but also empirical evidence with disastrous medical and social effects confirm that the problem is relevant.

There are numerous cases in history when drugs were responsible for the deaths of many people:

- USA, 1937: 107 people died after taking Elixir Sulfanilamide. The deaths were caused by DEG used as a solvent for the drug. The tragedy spurred the Federal Food, Drug, and Cosmetic Act, which tightened the requirements for preclinical safety studies [5];
- Haiti, 1995–1996: paracetamol syrup based on DEG-contaminated glycerin was the cause of a large outbreak of acute renal failure deaths among over 80 children [6];
- Panama, 2006: massive poisoning with cough syrups, which lead to numerous deaths. Cheap technical-grade glycerin contaminated with DEG was used to manufacture the medicines [7].

The largest recent outbreak occurred in 2022–2023 when more than 300 children in Gambia, Indonesia, Uzbekistan and other countries died of acute kidney injury, associated with contaminated cough syrups and antipyretics [8–10]. India has also declared cough syrups containing DEG and EG as toxic following the deaths of children in October 2025. The World Health Organization (WHO), which issued a series of global health alerts, and regulatory authorities around the world responded immediately [11, 12]. Thus, the issue, which is not local but global, requires a systemic response, including stricter regulatory controls and development of new analytical solutions.

The goal of this review is to systematize data about classical and modern methods for determination of EG and DEG and justify the critical need to introduce into practice the screening methods that can prevent similar catastrophes in the future.

1. CLASSICAL AND REFERENCE METHODS OF ANALYSIS

The global scientific and regulatory community uses chromatographic methods for reliable quantification of EG and DEG in pharmaceuticals due to their selectivity, accuracy, and sensitivity [13].

1.1. Gas chromatography with the flame ionization detector (GC-FID)

The CG-FID method is a primary method regulated in the United States Pharmacopeia (USP), European Pharmacopoeia (Ph. Eur.) and the State Pharmacopoeia of the Russian Federation (SPRF) to test whether glycerol, propylene glycol and other related substances contain EG and DEG [14–16].

During the GC-FID analysis, a sample is subjected to derivatization (for example, silanization) before entering the chromatographic column to improve volatility and chromatographic performance.

The mixture components are separated based on their differing distribution coefficients for a mobile phase (carrier gas) and a stationary phase inside the column. Detection is carried out with a flame ionization detector that uses a hydrogen-fueled flame to ionize organic compounds, ensuring high sensitivity of the method.

Modern GC-FID methods can achieve a limit of quantitative determination (LOQ) of 0.01%, which is ten times lower than the 0.1% permissible threshold for EG and DEG set by regulatory bodies. The methods provide excellent reproducibility and linearity over a wide concentration range, making them suitable for quantitative analysis in various matrices [17]. The advantages of the method include high selectivity, reliability, accuracy of quantitative analysis, and wide acceptance by regulatory authorities. The GC-FID method, however, has certain limitations such as high cost of equipment, need in skilled personnel, and a lengthy sample preparation process, including the stage of derivatization. Moreover, the stationary equipment used hinders on-site, field, or remote analyses.

1.2. Gas Chromatography-Mass Spectrometry (GC-MS)

Gas Chromatography-Mass Spectrometry (GC-MS) is justifiably considered the “gold standard” for confirming the authenticity of toxic impurities and solving complex analytical problems.

After being separated by the chromatographic column, the individual components of a sample enter the mass spectrometer, where they are first ionized, then fragmented, and finally detected by their mass-to-charge ratio. A mass spectrum from the GC-MS analysis serves as a unique “fingerprint” for a molecule, allowing for high-accuracy identification, even in complex mixtures.

The method is widely used to unambiguously confirm the presence of ethylene glycol and diethylene glycol in samples when there are doubts about the GC-FID results, as well as to analyze complex matrices, where the peaks of impurities may overlap with the peaks of other components [18].

The main advantages of the method include exceptional selectivity and sensitivity, as well as the ability to run both non-target analysis in full scan mode and target ion monitoring for increased sensitivity to target compounds.

The method, however, has significant limitations. Thus, the equipment characterized by high purchase and operation costs requires highly qualified operators.

2. THE NEED FOR SCREENING SOLUTIONS AND WHO INITIATIVE

Though classical and reference laboratory methods have a high analytical accuracy, they are not without the limitations such as high cost and limited sensitivity. GC-MS equipment can cost hundreds of thousands of US dollars, and single analyses often take several hours. The economic and logistical demands of managing every raw material and finished product batch are often impractical, especially for businesses in low- and middle-income countries. Meanwhile, the use of poor-grade or adulterated raw materials in these regions is a high-risk concern. It was clearly demonstrated through the tragic incidents in 2022–2023.

The WHO that had recognized the problem developed a Target Product Profile (TPP) for screening devices to detect DEG and EG contamination in medicines and excipients [19]. The regulatory document, which is currently seeking public comments, provides information about the minimum and preferred technical specifications for two categories of analytical devices for different levels of the supply chain.

The first category of TPPs is intended for high-level administrative bodies like national regulatory authorities, sanitary, and customs services. These systems have high analytical accuracy, ability to quantify trace impurities and integrate with software for registration and reporting.

The second category focuses on the product's direct application at the lower level of the chain, such as on production sites, in pharmacies, or within medical organizations. The devices have to be portable, easy to operate (including detected/not detected issues), have low cost of analysis, autonomous power without a connection, and no consumables.

The WHO Target Product Profiles (TPPs) include the following indicators for the key requirements to a medical product. Detection limit: the qualitative method must detect an analyte at concentrations as low as 0.1% (weight), while the quantitative method must be able to reliably quantify it at concentrations as low as 0.03% (weight).

Analytical performance: to pass, the qualitative test with a threshold of 0.1% should have at least 95% of sensitivity and at least 85% specificity.

The time characteristics for the analysis are less than 2 hours to obtain a result, while the optimal interval is under 10 minutes.

Portability: The device must be mobile and suitable for use outside the laboratory.

Economic parameters: the equipment cost should be significantly less as compared to gas chromatography-flame ionization detector (GC-FID) systems and have minimal costs per analysis without expensive consumables.

The devices that correspond to the TPPs can provide for the multi-layered control. It consists of fast and cheap screening of all incoming batches of raw materials and selected batches of finished products on site, followed by sending "suspicious" samples to accredited laboratories where they can be confirmed with reference methods.

3. PERSPECTIVE SCREENING METHODS

Active research in the field of screening technologies that correspond to the WHO TPP is being underway.

- Raman spectrometry uses the inelastic scattering of monochromatic light creating a unique spectral "fingerprint" of molecules. Modern portable Raman spectrometers, including surface-enhanced Raman spectroscopy (SERS) devices, can rapidly detect EG and DEG [20]. The advantages of the method include minimal sample preparation, non-destructive analysis, and screening through transparent packaging [21]. The main problems include development of effective substrates for SERS and algorithms for reliable signal isolation of target analytes against the background of a complex matrix of dosage forms.
- NMR spectroscopy — compact low-field NMR spectroscopy in particular — offers an integrated solution for analyzing mixtures by providing fast, minutes-long results with minimal sample preparation. This technique also allows for the simultaneous detection of EG, DEG and a basic compound (glycerol) using unique spectra [22]. The main objectives are to reduce the cost of instruments and simplify the interpretation of spectra for untrained users.
- Portable analytical systems: small-sized gas chromatographs combined with less energy-intensive detectors are being developed. The systems offer sufficient sensitivity and selectivity despite a smaller size and low cost.
- Thin-layer chromatography (TLC) is a simple and cost-effective technique for detecting ethylene glycol (EG) and diethylene glycol (DEG) impurities in raw materials and liquid dosage forms. It is ideal for situations with limited incoming control resources.

  The procedure involves applying a sample previously diluted with methanol to a silica gel plate, using elution in a solvent system, like a mixture of toluene–acetone–ammonia, and then visualizing them with a detecting agent like iodine vapor (in the presence of starch) or a strong oxidizing agent such as potassium permanganate. The method separates EG/DEG from glycerol, propylene glycol, and matrix carbohydrates. The staining technique has a detection limit of approximately 0.1% (weight percent) and a total analysis time of 20–60 minutes. The main advantages of TLC are low cost, portability and quick development time. It also allows for preliminary screening of samples at a regulatory threshold of ≤ 0.10%. Limitations include semi-quantitative nature of determination, reproducibility and sensitivity being affected by the matrix composition, need in standardizing conditions and using reference compounds because closely related glycols have similar chromatographic mobilities (Rf). All positive or borderline results must undergo confirmation using reference techniques such as gas chromatography with a flame ionization detector (GC-FID) or gas chromatography–mass spectrometry (GC-MS) [23].
- Biosensory and colorimetric methods: They are the most promising for creating cost-effective and easy-to-use test systems (similar to test strips). The principle of action is based on using enzymatic reactions with the formation of a colored product or on the specific binding of antibodies to their targets (immunochromatographic analysis). Achieving high sensitivity and minimizing interference from the sample matrix are crucial when the test systems are developed.
- Fourier transform infrared spectroscopy (FTIR): modern portable FT-IR spectrometers allow for rapid analysis of pharmaceutical products. The method requires specialized algorithms of chemometric analysis to determine EG and DEG impurities [24, 25].
- Microfluidic (labs-on-a-chip) platforms: the systems are of particular interest. Such systems make it possible to automate sample preparation and analysis, minimize reagent consumption, and ensure high reproducibility of results [26].

4. COMPARATIVE ANALYSIS OF ETHYLENE GLYCOL AND DIETHYLENE GLYCOL DETECTION METHODS

Table compares the key analytical and operational parameters of EG and DEG analysis methods. The comparison was based on the principle of action, main advantages and limitations, estimated cost, and portability. The parameters are listed in a decreasing order of sensitivity.

According to the table, a method of analysis is selected based on specific control tasks.

Reference methods (GC-MS, GC-FID) provide the highest sensitivity, but require significant resources. Screening methods (Raman and IR-Fourier spectroscopy, thin-layer chromatography) have reduced sensitivity, but offer advantages

Table. Comparison of some methods of analysis of ethylene glycol (EG) and diethylene glycol (DEG)

Method	Principle of action	Advantages	Limitations	Estimated cost	Portability
GC–MS	Gas Chromatography-Mass Spectrometry	High specificity, gold standard	Expensive to purchase and maintain	Very high	Low
GC-FID	Gas Chromatography-Flame Ionization Detector	High selectivity, quantitative analysis	Requires derivatization, stationary equipment	High	Low
Raman spectroscopy	Inelastic light scattering	A non-destructive and minimal sample preparation technique	The interfering effect of the matrix	Medium (SERS — high)	High
TLC	Elution in a solvent system on a silica gel plate	Simple analysis, low cost, portability	The interfering influence of the matrix, standardization of conditions	Low	High
Fourier transform infrared spectroscopy	Infrared absorption	Rapid analysis, portable devices	Low selectivity	Low	Medium (portable versions are available)

in speed, cost, and the ability to be used in the field. It is optimal to use a multi-level approach, combining timely screening of all batches with selective confirmation of the results by reference methods.

CONCLUSION

Contamination of medicines with ethylene glycol (EG) and diethylene glycol (DEG) is a serious global health challenge. To tackle it, a multi-level approach covering the following key directions is required.

1. Tightening regulatory requirements through mandatory testing of high-risk raw materials and implementation of the quality control recommendations below:
   - mandatory identification testing using specific methods;
   - testing samples from each container of each batch of raw materials;
   - setting a limit of no more than 0.1% for EG and DEG content;
   - mandatory verification of the supply chain and certificates of analysis.
2. Development of modern labs through equipment of accredited labs with modern reference equipment (GC-FID, GC-MS) and preparation of qualified personnel.
3. Introduction of modern screening solutions that correspond to the WHO TPPs to form a multi-leveled quality control system at all stages of the pharmaceutical supply chain.

The use of portable analytical techniques such as Raman spectroscopy is of particular concern as it allows to do as follows:

- rapid analysis without destroying the sample;
- detection through transparent packaging;
- minimal sample preparation;
- high-precision identification of molecules by spectral fingerprints.

Good perspectives of this approach are confirmed by active research in this field, including the one aimed at the development of specialized screening methods for the Russian pharmaceutical market [27].

The tragic mass poisoning should result in international consolidation of efforts of regulatory authorities, manufacturers of diagnostic equipment and the scientific community. Joint collaboration and implementation of modern analytical solutions will allow for development of a reliable pharmaceutical safety system warranting that a patient's life will totally depend on drug effectiveness but not purity.

Exhibit. Detailed analysis of excipients with a high risk of ethylene glycol and diethylene glycol contamination

Excipient	Contamination risk	The main sources of risk	Regulatory documentation
Glycerol	Very high	Byproduct in the biodiesel manufacturing process, incomplete purification	USP Monograph: Glycerin Ph. Eur. 07/2022:0496 ФС.2.2.0006.15 (SPRF)
Propylene glycol	High	Technological impurities from the manufacturing process, falsification	USP Monograph: Propylene Glycol Ph. Eur. 01/2025:0430 ФС.2.1.0169.18 (SPRF)
Polyethylene glycol (macrogol)	Medium-high	Residual monomers, technological impurities	USP Monograph: Polyethylene Glycol Ph. Eur. 01/2005:1123 ФС.2.1.0127 (SPRF)
Sorbitol	High	Incomplete hydrogenation, impurities of raw materials	USP Monograph: Sorbitol Solution Ph. Eur. 01/2005:0436 SPRF: the project is in progress

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LEGAL AND ETHICAL FRAMEWORK FOR DISTANCE RETAIL SALES OF MEDICINES

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Distance retail sale of medicines is a mechanism that makes pharmaceutical care more accessible. The objective of the study is to analyze the legal and ethical framework surrounding online retail sales of medicines. The subject of the study is the regulation of ethical standards for consulting in online retail sale of medicines. The study methodology involved first identifying the conditions for remote drug sales and then determining the requirements for this trade method. The research materials included regulatory documents and scientific publications focused on the remote retail sale of medicines. The methods of content analysis, comparison and generalization were used. During the study it has been found out that the current legal frameworks govern how pharmacists comply with ethical standards, specifically addressing the remote sale of medicines. It has been established that, regardless of the method of ordering, information about medicines is provided to customers by a qualified employee of a pharmacy on a professional basis.

Key words: medicine, ethics, distance selling, pharmacist

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ПРАВОВОЕ РЕГУЛИРОВАНИЕ ЭТИЧЕСКИХ АСПЕКТОВ РОЗНИЧНОЙ ТОРГОВЛИ ЛЕКАРСТВЕННЫМИ ПРЕПАРАТАМИ ДИСТАНЦИОННЫМ СПОСОБОМ

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Розничная торговля лекарственными препаратами (ЛП) дистанционным способом — один из механизмов обеспечения доступности лекарственной помощи населению. Цель исследования — анализ правового регулирования соблюдения профессиональной этики при розничной торговле ЛП дистанционным способом. Предметом исследования стало регламентирование этических норм консультирования при осуществлении розничной торговли ЛП дистанционным способом. Методика исследования включала выявление условий осуществления розничной торговли ЛП дистанционным способом, далее определены требования при реализации данной формы торговли ЛП. Материалами исследования послужили нормативно-правовые документы, регулирующие розничную торговлю ЛП дистанционным способом, научные публикации. Использовались методы контент-анализа, сравнения и обобщения. В результате исследования установлено, что в настоящее время в правовом поле регламентируется соблюдение этических норм фармацевтическими работниками, в том числе при розничной торговле лекарственными препаратами дистанционным способом. Установлено, независимо от способа заказа предоставление информации о лекарственных препаратах покупателям осуществляется квалифицированным работником аптечной организации на профессиональной основе.

Ключевые слова: лекарственный препарат, этика, дистанционная торговля, фармацевтический работник

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Distance retail sale of medicines is a mechanism that makes medical care available. Many authors are currently researching the remote sale of medications. E-commerce is established to expand access to medical care, especially for such populations as retired people, disabled people, families with young children, and people with limited mobility [1, 2]. The advantages of remote services for citizens have been examined. Thus, customers appreciate online medicine purchases for saving time (80.7%), the possibility of ordering from home (67.2%), shopping from anywhere and at any time that is convenient for them (58.8%), the ability to compare a wide range of products (53.8%) and make all purchases at once (52.1%), as well as for various promotions, promo codes, and loyalty programs (45.4%) [3].

Other authors considered regulatory control of distance selling of medicines focusing on changes in the legislation and development perspectives. New methods of drug retailing require increased attention to consumer protection [4, 5].

According to the conducted research, distance purchase of medicines increases patient risk by allowing for independent selection, bypassing medical and pharmaceutical oversight [6]. A study found that 93.2% of people believe it's important to consult with a pharmacy specialist when buying medicines [3].

Thus, distance retail sale of medicines can expand access to medicinal products, which aligns with the ethical principles of fairness and protection of public health. It is important to ensure proper consumer protection by providing qualified advice, given the high demand for personal support when purchasing medicines.

Table. Information provided to customers using distance retailing of medicines

Order of the Ministry of Health of Russia dated 04/29/2025 No. 259n	Decree of the Government of the Russian Federation dated 05/16/2020 No. 697
rules of storage at home	rules of storage
food-**drug interactions**	drug interactions
use of medicinal products, including: – route of administration, – dosing regimen	drug indications
therapeutic action	retail price
contraindications	expiry date
information about the availability of medicinal products with the same international nonproprietary name	dispensing requirements
information about the availability of medicinal products with a lower price	–

Professional activities in drug provision require pharmacists to adhere to specific moral and ethical standards in their work [7]. Professionalism is a key principle of ethics. Licensing requirements are a type of educational and qualification requirements for employees [8]. Also, compliance with the principles of medical ethics and deontology by pharmacists is regulated by good pharmacy practice (GPP) [9]. It is crucial to study these aspects during consultation when selling medicines remotely.

The purpose of the study was to analyze the legal regulations governing the professional ethics of distance retail sales of medicines.

The object of the study was distance retail sale of medicines. The subject of the study is the regulation of ethical standards for consulting during distance retail drug sales.

PATIENTS (MATERIALS) AND METHODS

The research methodology first identified the conditions for distance pharmaceutical selling, then established the requirements for this type of business. The research materials consisted of regulatory documents that govern the online retail sale of medicines and scientific publications. The combination of content analysis, comparison, and generalization was used.

RESULTS AND DISCUSSION

A comparative analysis of “a pharmaceutical activity” and “a pharmacy” shows they both encompass the retail sale of medicines, including remote sales through online platforms. However, online retail is not currently considered part of a pharmacist’s official responsibilities [10, 11].

In accordance with GPP, the head of a retail entity must ensure that employees obtain initial and subsequent training on the requirements to pharmacies selling medicines online through various retail services as per the approved plan [9, 12]. Consequently, the pharmaceutical employee of the pharmacy is charged with such duties.

Pharmacists must provide complete and reliable information about medicines, even when retailing remotely. In this regard, regulatory documentation requirements to information were analyzed (table).

The table shows that the scope of information provided to a buyer during the retail sale of medicines, including distance selling, varies according to the submitted regulatory documents. Thus, Order No. 259h covers more parameters that have to be taken into consideration when informing buyers.

A distance-selling pharmacy must have as follows:

– a web-site or a mobile app;
– an agreement with the owner of an aggregator that provides information about goods or services under the Russian law on consumer rights protection. In this case, a pharmacy acts as the seller, so the purchase and sale agreement is concluded on its behalf.

It is stated that regulations for the remote retail sale of medicines generally cover the receipt, placement, storage and delivery of orders for medicines, while explicitly excluding prescription medicines [12].

Remote orders for medicines can be received through several ways:

– when the buyer contacts a pharmacy through the website (mobile application) of the pharmacy;
– when the owner of the aggregator is contacted through the website (mobile application) of the owner;
– by calling the medicine ordering service or the help desk of another structural unit of the pharmacy that accepts drug orders.

Confidentiality of the buyer’s personal data is an ethical principle that requires both the pharmacy and the aggregator to follow the laws of the Russian Federation.

When taking remote orders for medicines, an employee of the pharmacy or an aggregator must inform the buyer about the drug’s indications, retail price, expiration date, dispensing conditions, storage rules, and interactions with other drugs.

The procedure for informing buyers varies depending on how they apply to order medicines (Fig.)

A pharmacy is responsible for informing the public about a medicine, regardless of how it is ordered, because it is the seller.

CONCLUSIONS

Regulatory and legal documents govern how pharmaceutical workers comply with the ethical standards, especially in case of distance retail selling of medicines. So, customers receive professional, qualified advice on medications regardless of how they order them.

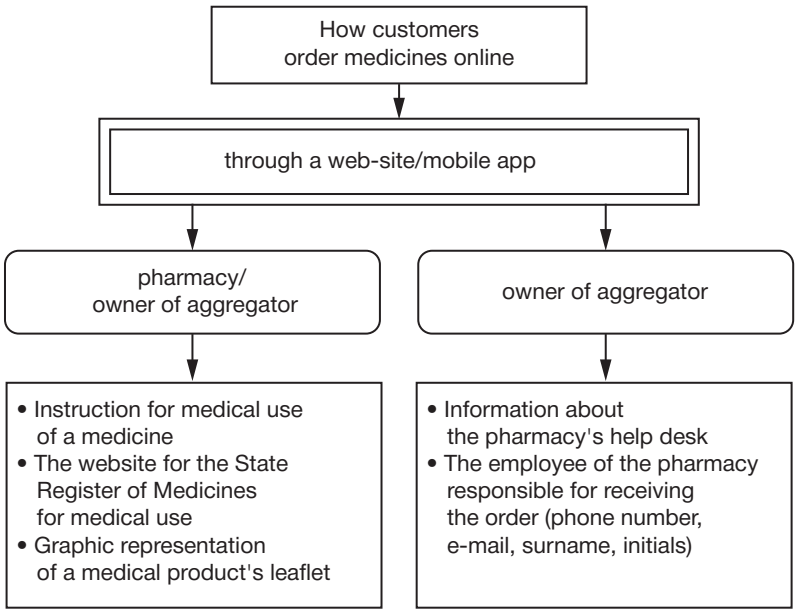

Fig. Ways of ordering medicines online and informing procedure during distance ordering of medicines

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THE COCHRANE COLLABORATION'S CONTRIBUTION TO THE DEVELOPMENT OF PRINCIPLES OF INTEGRITY IN RESEARCH PRACTICE

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This article is one in a sequence of publications in the Journal of Medical Ethics focused on the integrity of healthcare research. Our first article in the series on integrity in modern biomedical science briefly reviewed the main stages of the global think tank development calling to attention of a wide range of specialists from local ethical committees, editorial boards of biomedical journals, and experts of scientific funds who determine the research priorities and fund studies. In this article, we concentrated on the specific contribution and pioneering function of the Cochrane collaboration in developing scientific research integrity principles.

Keywords: conflict of interest, integrity, medical research, systematic reviews, clinical practice guidelines, Cochrane, Cochrane Library

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ВКЛАД КОКРЕЙНОВСКОГО СОТРУДНИЧЕСТВА В РАЗВИТИЕ ПРИНЦИПОВ ДОБРОСОВЕСТНОСТИ ИССЛЕДОВАТЕЛЬСКОЙ ПРАКТИКИ

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Настоящая статья является продолжением серии публикаций в журнале «Медицинская этика» по проблеме добросовестности, или целостности — честности — порядочности исследовательской практики в здравоохранении. В нашей первой статье из серии статей о проблемах добросовестности в современной биомедицинской науке мы кратко представили основные этапы развития мировой научной мысли в этом направлении, обращая внимание широкого круга специалистов локальных этических комитетов, редакционных коллегий биомедицинских журналов, экспертов научных фондов, определяющих приоритеты и финансирование исследований. Здесь мы сконцентрировали внимание на конкретном вкладе и пионерской роли Кокрейновского сотрудничества в развитие принципов добросовестности научных исследований.

Ключевые слова: конфликт интересов, добросовестность, медицинские исследования, систематические обзоры, клинические рекомендации, Кокрейн, Кокрейновская библиотека

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The establishment of the Cochrane Collaboration has dramatically advanced research integrity in medicine, pharmacy and healthcare. Cochrane has always been at the forefront of the scientific thought within the health sciences around the globe. Cochrane's policies aim to clarify conflicts of interest (COI) and key aspects of their assessment. In addition, management of COI should become the main principle and a mandatory requirement for the integrity of research [1].

At Cochrane, a conflict of interest is a set of circumstances and conditions that creates a risk that professional judgment or actions regarding a primary interest (the patient's health, validity of the study) will be unduly influenced by a secondary interest (for example, financial).

Cochrane is committed to minimizing the impact of conflicts of interest. Thus, its work is internationally recognized as the benchmark for high-quality medical information.

Cochrane's systematic reviews and core values of independence, transparency, and research integrity are supported by its strict policies on reporting and managing potential conflicts of interest [2].

ADHERENCE TO CONFLICTS OF INTEREST POLICIES AT COCHRANE

Cochrane enforces a very strict Conflict of Interest (COI) Policy for the Cochrane Library Content. It requires a full disclosure of potential conflicts and prohibits individuals with certain conflicts from participating in review development and update [2].

The updated COI policy for Cochrane review authors and the Cochrane Library Content came into force on October 14, 2020. Many Cochrane reviews were already underway

before the date. As applying a new policy to already published Cochrane Reviews would be overly burdensome for editorial teams and unfair to existing authors, the 2014 Conflict of Interest Policy continues to apply to those Cochrane Reviews (and their updates) that had begun development before the 2020 policy was introduced [3].

Cochrane has established strict regulations and a comprehensive system of rules regarding COI for all its Groups. These rules and regulations were originally published in 2014 and updated in March 2022. They apply to Geographic groups (for example, Cochrane Russia, Cochrane China), Methods groups and Thematic groups, sites and evidence synthesis units. These groups are not allowed to accept funds from commercial sponsors or sources that have a financial interest in the areas covered by the Cochrane Library. Cochrane Groups that violate this policy may be deregistered by the Cochrane Governing Board [2–3].

MANAGEMENT OF COI AT COCHRANE

The funding sources of Cochrane Groups are monitored annually by the Cochrane leadership. The sources should be unconditionally consistent with Cochrane conflict of interest policies.

All queries about identifying and managing potential conflicts, implementation of rules, regulations, and conditions for using COI policies should be submitted to the Editorial Group dealing with research integrity and conflicts of interest. The group was created to impartially assess potential conflicts of interest and make timely recommendations [2].

STUDYING THE IMPACT OF COI IN COCHRANE SYSTEMATIC REVIEWS

Cochrane researchers have shown in a series of Cochrane reviews that the impact of conflicts of interest on research practice and presentation of research results is enormous. The first in the series Cochrane review about industry sponsorship and research outcomes, which was published in 2017 and translated into 13 languages, was used in four clinical guidelines. It has an All-metric score of 863 [4].

The review found that industry-sponsored (sponsored by manufacturers of medicinal products and medical devices) research of medical interventions such as drugs and devices is more likely to conclude that the product of the sponsor is effective than studies not funded by industry. This is due to bias that cannot be explained using standard Cochrane review methods or risk of bias assessment tools for bias or shift. It is important to note that the results of clinical trials of medicines and medical devices influence the decisions that doctors make when treating patients. Clinical trials are often funded by manufacturers of the tested products. Companies can also conduct the trials themselves. In the updated review, the authors were the first to study the impact of industry funding on clinical trials' conclusions [4–5].

The authors of this review carried out a comprehensive search for all relevant papers of studies published from 2010 to 2015 and included 75 studies with funding-related data [4].

On the basis of the synthesis of the results of included clinical trials, the review found that clinical trials funded by industry sponsors (manufacturers) reported product effectiveness more often with a risk ratio (RR) of 1.27 (95% confidence interval (CI) ranging from 1.17 to 1.37), without significant difference in harm, with favorable overall conclusions, and recorded risk ratio of 1.34 (95% CI ranging from 1.19 to 1.51). The results were compared with those from trials not funded by industry.

The authors of this review found no differences in standard methods that could increase the risk of bias between industry-funded and non-sponsored clinical trials, except for the blinding procedure. Industry-funded studies were more likely to report satisfactory blinding and showed less agreement between results and conclusions than non-industry funded studies (RR 0.83, 95% CI from 0.70 to 0.98).

Sponsored trials of medicinal products and medical devices equally showed a greater benefit for the sponsoring manufacturer's product and had certain methodological shortcomings. Thus, industry-sponsored studies tend to be biased in favor of the sponsor's products [4–5].

Systematic reviews have been considered the best way to present information about a set of clinical trials addressing a specific clinical or healthcare issue. The reviews significantly influence clinical decision-making and choosing the most effective interventions. Thus, reliability and confidence are crucial for the systematic reviews.

However, in some cases, systematic reviews are funded by pharmaceutical or other manufacturing companies with a financial interest in the review's results and conclusions when they produce the drug or device being tested. In other cases, systematic reviews are carried out by researchers having a personal financial interest in specific results or conclusions. It happens, for example, when the author consults the company that manufactures the product being tested in the review. Such financial conflicts of interest can impact development of systematic reviews and presentation of their results.

Cochrane researchers examined the issue in detail in the Cochrane review regarding financial conflicts of interest in systematic reviews: associations with results, conclusions, and methodological quality [6].

The research has found how often systematic reviews with financial conflicts of interest presented conclusions more favorable to the intervention (product) being studied than those without conflicts. They also assessed differences in methodological quality of systematic reviews with and without financial conflicts of interest.

Having compared systematic reviews with and without financial conflicts of interest (COI) from seven included trials, the authors discovered that systematic reviews with COI tended to have more frequent (almost twice as high) conclusions in favor of the product in conflict with RR of 1.98 (95% CI ranging from 1.26 to 3.11) as compared to those without COI. Using synthesized results of four studies, the authors of this Cochrane Review showed that the methodological quality in systematic reviews with financial conflicts of interest was lower [6].

Thus, authors of the Cochrane review have concluded that systematic reviews with financial conflicts of interest, often funded by industry funding or with industry authorship, tend to have lower methodological quality and present more favorable conclusions than those without such conflicts. Thus, the authors of the study recommend that users of systematic reviews — including patients, doctors, guideline developers, and researchers — prioritize the reviews that have no financial conflicts of interest of their authors.

Authors should be cautious when studying and interpreting systematic reviews, especially when only those with a COI are available.

CONFLICTS OF INTEREST IN CLINICAL PRACTICE GUIDELINES

Conflicts of interest are highly relevant for clinical trials, systematic reviews and clinical practice guidelines.

This problem was first studied in a Cochrane's Review entitled "Conflicts of interest in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews: associations with recommendations" [7].

Clinical practice guidelines can be presented in various documents. These can be individual clinical practice guidelines (recommendations) or published journal articles. Clinical practice guidelines represent a set of provisions and assertions that recommend how to diagnose, prevent and treat patients with a pathology. Clinical practice guidelines must be based on the best available evidence.

Unfortunately, healthcare professionals with a COI in relation to a certain product or intervention commonly act as authors of publications containing clinical guidelines. For example, an author of clinical practice guidelines can also consult the manufacturer of a medicinal product or a medical device. The conflict of interest can influence the content of the guidelines (recommendations).

Meanwhile, developers of clinical practice guidelines can have non-financial COI as they belong to certain medical professions or due to ambitious career-drive conflict of interest.

Authors of Cochrane methodological review that included 21 trials examined financial and non-financial COI and their relation to the suggestions from clinical practice guidelines, advisory committee reports, opinion pieces, and narrative reviews.

The authors have shown that financial COI are associated with positive recommendations. In other words, the clinical practice guidelines compiled by persons with financial COI more likely contained positive recommendations as compared to those made by experts without COI. The impact of non-financial COI on clinical practice guidelines was examined in one study only, and similar results were obtained confirming a shift towards positive or favorable recommendations in relation to certain interventions (technologies).

Authors of this review suggest that patients, doctors and people taking healthcare decisions should primarily use the clinical practice guidelines prepared up by experts without any conflict of interest [7–8].

CONCLUSIONS

Thus, modern healthcare, medical education and biomedical research practice come across more and more complex signs of undue practices in research and reporting of results while seemingly striving to use scientifically substantiated facts (evidence) with reference to meta-analyses and systematic reviews.

Widespread financial dependence on industry introduces a commercial bias in scientific data, medical education, and clinical practice. The bias results in exaggeration of benefit and underestimation of harm.

It is essential to differentiate between conflict and conflict-free biomedical experimental and clinical trials, meta-analyses, systematic reviews, and clinical practice guidelines targeted at medical practice. Cochrane systematic reviews are still regarded as the gold standard in research quality and research integrity.

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PHARMACOGENETIC TESTING: ETHICAL CHALLENGES AND SOLUTIONS

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The article reviews ethical and legal hurdles of integrating pharmacogenetic testing into personalized medicine. The aim of this publication was to systematize key ethical problems in clinical pharmacogenetics and find possible solutions in Russian legislation. It was an analytical review study that used a systematic analysis of scientific literature combined with comparative legal analysis of national/foreign regulations. The risks of confidentiality violations and unauthorized reuse of genetic data, difficulties in obtaining informed consent and interpreting incidental findings, and a threat of genetic discrimination from employers and insurance companies are reviewed. It has been shown that a high cost of genetic tests increases the inequality of access to medical technologies and highlights major social injustice issues. It is concluded that clarifying the legal status of genetic data, developing special mechanisms to protect patients from stigmatization and discrimination, and introducing educational programs on pharmacogenetics and genetic counseling for medical professionals are essential.

Keywords: pharmacogenetics, genetic passport, personal data protection, genetic discrimination

Contribution of authors: Demarina SM — selection and analysis of literature, writing the text of the manuscript; Sirotkina AM — literature analysis, editing the manuscript text; Usolkin AA — selection and analysis of literature, writing the text of the manuscript; Dombrovskaya ED — literature analysis, editing of the manuscript text.

Compliance with ethical standards: This work is a review and does not involve human or animal subjects. The approval of the ethics committee was not required.

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ФАРМАКОГЕНЕТИЧЕСКОЕ ТЕСТИРОВАНИЕ: ЭТИЧЕСКИЕ ВЫЗОВЫ И ПУТИ ИХ РЕШЕНИЯ

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Статья посвящена этическим и правовым аспектам внедрения фармакогенетического тестирования в клиническую практику персонализированной медицины. Цель работы — систематизировать ключевые этические проблемы клинической фармакогенетики и обозначить возможные пути их урегулирования в российском здравоохранении. Исследование выполнено в формате аналитического обзора с использованием методов системного анализа научной литературы и сравнительно-правового анализа национальных и зарубежных нормативных актов. Рассмотрены риски нарушения конфиденциальности и несанкционированного вторичного использования генетических данных, сложности получения информированного согласия и интерпретации «случайных находок», а также угроза генетической дискриминации со стороны работодателей и страховых компаний. Показано, что высокая стоимость генетических тестов усиливает неравенство доступа к медицинским технологиям и порождает вопросы социальной несправедливости. Сделан вывод о необходимости уточнения правового статуса генетической информации, разработки специальных механизмов защиты пациентов от стигматизации и дискриминации, а также внедрения образовательных программ по фармакогенетике и генетическому консультированию для медицинских работников.

Ключевые слова: фармакогенетика, генетический паспорт, защита персональных данных, генетическая дискриминация

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Соблюдение этических стандартов: данная работа является обзорной и не предполагает проведения исследований с участием людей или животных. Одобрение этического комитета не требовалось.

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Modern medicine is undergoing a paradigm shift: from a standardized empirical approach of “one drug for all patients” to personalized therapy based on the individual characteristics of each patient. Pharmacogenetics ensures this transition. According to the research, genetic polymorphism accounts for 20 to 95% of patient variability in individual response to drugs. It means that two patients receiving the same dose of medication may experience different effects: one can have a complete recovery, whereas the other one can develop a serious adverse reaction. Pharmacogenetic testing for carriage of allelic variants of cytochrome P450 genes (CYP2C9, CYP2D6, etc.) has already been included in clinical guidelines and protocols of leading medical organizations.

To select the dose of Indirect-acting anticoagulants, data on the polymorphism of the CYP2C9 and VKORC1

genes are required. Thus, it is possible to select the optimal dose of warfarin, reducing the risk of bleeding by 30–40%. Without the test, a long period of dose titration is required, the cost of INR control increases, and the likelihood of thromboembolic complications is higher. In oncology, determining the status of the DPYD, TPMT, and NUDT15 genes is critically important for preventing fatal toxic reactions to chemotherapy [1,2]. Rapid genetic advancements often outpace legal and ethical frameworks. The genetic passport of a patient creates unprecedented bioethical challenges related to the storage and protection of "sensitive" genetic information, interpretation of results, accessibility of technologies and fairness of their distribution. The results of the genetic test are unchanged throughout life. They relate not only to patients, but also to their blood relatives and may have a prognostic value that goes beyond the current disease or the reason for the test.

The review purpose is to systematize the key ethical and legal hurdles of clinical pharmacogenetics and identify possible ways to resolve them.

CONFIDENTIALITY AND PROTECTION OF GENETIC DATA

The risk of unauthorized access to genetic information and its leakage belongs to major, acute ethical and practical challenges in pharmacogenetics. Genomic data are exceptional as they are unique for every person and allow to identify a personality even following formal anonymization. Unlike other types of medical information, genetic data disclose information not only about the patient, but also about his biological relatives, which creates additional ethical obligations to third parties [3, 4]. In the Russian Federation, genetic information is subject to Federal Law on Personal Data (No. 152-FZ) and is classified as a special category of personal data requiring the highest protection. There are gaps in legislation regarding the secondary use of genetic data for scientific purposes and their transfer [4, 5].

Biobanks and centralized databases of pharmacogenetic research create a dilemma between the need for an open exchange of scientific data under Open Science and the fundamental right of a patient to privacy and confidentiality of genetic information. Disclosure of information about a genetic predisposition to socially significant diseases (mental, oncological, neurodegenerative ones) can cause irreparable damage to a person's reputation and social status, and lead to refusal of employment or training. Ownership of genomic data is a complex issue. Who is the owner and manager of the genomic data — the patient, the medical organization that conducted the testing, or the laboratory? Ethical expertise requires a clear distinction between the rights of access and use of information for different purposes (personal use, scientific research, commercial purposes, government regulation), especially when using cloud technologies for storing data and transferring test results to third parties. Russia needs to develop specific laws for genetic info similar to the EU's GDPR (General Data Protection Regulation), which clearly defines the rights of patients, obligations of data warehouses and penalties for violations [6].

THE PROBLEM OF INFORMED CONSENT AND INCIDENTAL FINDINGS

The classic model of informed consent is not adapted for genetic testing. Patients struggle to understand probabilistic pharmacogenetic results, especially when they are more related to predispositions rather than diagnoses. Clinical practitioners struggle with complex genotypes especially in the presence of rare or previously undescribed allelic variants. How can I explain to a patient that he is a carrier of a CYP2D6 intermediate metabolizer and what it means for his treatment? Specialized genetic counseling and advanced genetic testing are often limited in Russia's public healthcare.

Incidental findings in research are ethically complex. Pharmacogenetic testing for the DPYD gene (to select a safe dose of chemotherapeutic drugs) can reveal genetic variants that, while not impacting drug metabolism, might signal predispositions to other serious hereditary conditions (familial hypercholesterolemia, early Alzheimer's disease). But do doctors have a legal and ethical duty to inform patients about significant, unexpected findings, even if not initially sought? And what should I do if there is no effective treatment or prevention for the identified predisposition? Can such information cause psychological harm to the patient, leading to unreasonable anxiety? International ethics committees (Nuffield Council on Bioethics, American Medical Association) tend to recognize the patient's right to "not know" about such findings, however, in clinical practice, this right often conflicts with the classic principle of medical ethics "do no harm" and the physician's duty to act in the patient's best interests [7, 8]. These issues are relevant in the field of reproductive medicine. When conducting preimplantation genetic testing to select an embryo without a hereditary disease (cystic fibrosis), the analysis may reveal that both partners are carriers for hemophilia B. Information about the carrier does not affect the IVF decision, but it is important for the future health of patients and their children. Should the doctor share this information? The answer is obvious — yes, but it takes time, a trained genetic counselor, and clear protocols of action [7, 8].

RISKS OF GENETIC DISCRIMINATION

The fear of genetic discrimination is a significant social and psychological hurdle to pharmacogenetics adoption in clinical practice. Genetic discrimination is defined as infringement of the rights of an individual based on information about his genome. In the context of pharmacogenetics, this can be manifested as refusal of insurance companies to conclude voluntary medical insurance or life insurance contracts, or in an increase in insurance premiums for people with an unfavorable metabolic profile, which implies high treatment costs [9].

The problem of labor discrimination is urgent. Employers may be interested in screening employees to identify predisposition to occupational diseases or predict frequent sick leaves. For example, carrying slow acetylator (NAT2) alleles significantly increases the risk of toxic effects from certain industrial chemicals. From an ethical point of view, it is unacceptable to use such data to refuse employment. In the United States, the GINA (Genetic Information Nondiscrimination Act) federal law has been in force since 2008, which explicitly prohibits the use of genetic information to make decisions about hiring, promotion, or dismissal. Similar laws exist in most developed countries of Europe and in Canada. The Russian Federation still lacks a specific law for genetic discrimination, although Article 19 of the Constitution of the Russian Federation guarantees equality of rights and freedoms regardless

of origin and other circumstances. It is necessary to develop legal mechanisms that clearly prohibit the use of pharmacogenetic data by third parties (insurers, banks, employers, educational institutions) and provide for real penalties for violations [9, 10].

SOCIAL JUSTICE AND ACCESSIBILITY OF TECHNOLOGY

Personalized medicine and pharmacogenetic testing create an ethical issue of inequality in healthcare based on access to genetic technologies. The cost in commercial laboratories varies from 5 to 50 thousand rubles, depending on the number of analyzed genes and technology. It is critical that most pharmacogenetic tests, even those with proven clinical significance (WHO classification levels of evidence A and B), are not covered by compulsory health insurance programs. It means that not all groups have an equal access to healthcare. Well-off patients receive access to safe and effective personalized therapy based on the results of pharmacogenetic testing and avoid dangerous adverse reactions, while socially vulnerable patients continue to be treated by empirical trial and error, at risk of adverse outcomes, including hospitalization, disability and mortality [11, 12]. The ethical principle of equity states that innovative and effective medical technologies should be available to all patients in need, regardless of their socio-economic status. This is especially true in oncology, cardiology, and psychiatry, where the cost of medical error or suboptimal selection of therapy is critically high.

CONCLUSIONS

Pharmacogenetics changes modern medicine by offering tools to personalized treatment. However, technological progress should not outpace ethical thinking. In our opinion, protection of genetic data confidentiality, prevention of discrimination, and ensuring equal access to innovations are still the key challenges.

To solve these problems, the following steps are necessary:

1) **Improvement of legislation:** consolidation of genetic information status and a direct ban on genetic discrimination.
2) **Medical education:** professional development for medical professionals in test interpretation and ethical counseling of patients.
3) **Infrastructure development:** creation of secure national biobanks and integration of validated tests into clinical guidelines and standards of care.

The balance between innovations and human rights protection is the main condition for ethically sound personalized medicine and pharmacogenetics in the Russian Federation.

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