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Научная статья / Research Article

Legal regulation of additive technologies in modern biomedicine

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Abstract. Research reveals the legal problems that arise due to the rapid pace of development of additive technologies (3D printing) in biomedicine (bioprinting). The purpose of the research is to analyze the legislation that defines the legal regime of additive technologies, identify the main gaps in regulation, carry out a comparative legal study, which allows to formulate recommendations to improve Russian legislation. Special strategies are used as an object of comparative research; they contribute to fix the priority development of 3D printing. The employed methods are as follows: the method of analysis of legal regulation, comparative legal and formal legal. Results. Attention is paid to the main trends and risks of progress in this direction, which are reflected in decentralization of production; improving its efficiency and reducing waste; reduction of development time and their introduction into mass production with a simultaneous rise in quality of the finished product; expanding the population's access to material goods; minimizing the state control. Particular attention is paid to the legal assessment of the applicability of bioprinting in transplantology, the manufacture of implants, surgical planning, and the use of printed organs for experiments. Conclusions: when adjusting the legal framework, institutional readiness should be taken into account — the ability of the entire Russian healthcare system to use additive technologies properly (which will require significant changes in healthcare legislation). An independent direction is the use of bioprinting in the testing of drugs. 3D printing creates small organ-like structures (they are called organoids) on which experiments can be carried out for the screening of pharmaceuticals. This will require changes in the legal regime for the circulation of medicines, as well as the main functions of the state regulator (the Russian Ministry of Health and Roszdravnadzor). It is noted that additive technologies make it possible to manufacture medicines, but world experience indicates a cautious attitude towards this type of production. Research argues for the need to follow a risk-based approach in the legal regulation of bioprinting, as well as to introduce the general approach of Hospital Exemption (pharmaceutical exclusion) used in the countries of the European Union, as well as some other countries aimed at the development of regenerative medicine.

Key words: additive technologies, bioprinting, biomedicine, legal regulation, organ donation, regenerative medicine

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The participation of the authors: *Romanovskaya O.V.* — introduction, concept, scientific analysis of materials; *Romanovskiy G.B.* — scientific leadership, theoretical substantiation of the study, generalization of the results obtained, conclusion

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Правовое регулирование аддитивных технологий в современной биомедицине

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Аннотация. Раскрываются юридические проблемы, которые возникают в силу быстрых темпов развития аддитивных технологий (3D-печати) в биомедицине (биопринтинг). Цель исследования — проанализировать законодательство, определяющее правовой режим аддитивных технологий, выявить основные пробелы в регулировании, осуществить сравнительно-правовое исследование, на основе которого сформулировать рекомендации по совершенствованию российского законодательства. В качестве объекта компаративистского исследования выступили также специальные стратегии, согласно которым закрепляется приоритетное развитие 3D-печати. Основу исследования составили методы: анализа нормативно-правового регулирования, сравнительно-правовой и формально-юридический. Рассмотрены основные тренды и риски прогресса в данном направлении: децентрализация производства; повышение его эффективности и сокращение отходов; сокращение времени разработок и их внедрения в серийное производство с одновременным ростом качества готового изделия; расширение доступа населения к материальным благам; минимизации государственного контроля. Особое внимание уделено правовой оценке применимости биопритинга в трансплантологии, изготовлении имплантов, хирургическом планировании, использовании напечатанных органов для проведения над ними экспериментов. Выводы: при корректировке правовой базы следует учитывать институциональную готовность — способность всей системы российского здравоохранения использовать аддитивные технологии надлежащим образом (что потребует значительных изменений законодательства в сфере здравоохранения); самостоятельным направлением выступает применение биопринтинга при тестировании лекарственных препаратов; с помощью трехмерной печати создаются органоподобные структуры небольшого размера (они получили название органоиды), на которых можно проводить эксперименты для скрининга фармацевтических препаратов; это потребует изменений правового режима оборота лекарственных препаратов, а также основных функций государственного регулятора (Минздрава России и Росздравнадзора). Отмечается, что аддитивные технологии позволяют изготавливать лекарственные средства, но мировой опыт свидетельствует об осторожном отношении к такому типу производства. Отстаивается необходимость следования риск-ориентированному подходу в правовом регулировании биопринтинга, а также внедрения общего подхода Hospital Exemption (фармацевтического исключения), используемого в странах Европейского Союза, а также некоторых других странах, нацеленных на развитие регенеративной медицины.

Ключевые слова: аддитивные технологии, биопечать, биомедицина, правовое регулирование, донорство органов, регенеративная медицина

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Introduction

Additive technologies increasingly occupy the top of the agenda when discussing the prospects for modern progress. However, this term is not known to the mass consumer. The most common term that characterizes them is three-dimensional printing, or 3D printing. This is a production method in which the necessary three-dimensional objects are produced in layers by fusing or spraying materials such as plastic, metal, ceramics, various powders, and liquids. It has revolutionary implications because it does not require a large production facility, but it can result in complex technological products. The world's leading car showrooms are already presenting first 3D-printed cars, some of which may qualify for mass production. In 2015, in Geneva, the German company EDAG presented the Light Cocoon concept car, almost entirely printed on special printers[1]. In 2019, the American researcher S. Backus in his own garage (with his 11-year-old son) "printed" a Lamborghini Aventador sports car, spending about 20 thousand dollars on it (with its factory cost of 300 thousand dollars)[2]. For the first time, 3D printing of houses has been tested (both in Russia and abroad[3]).

Technology does not stand still. Living cells are being used as a material, which has become the basis of bioprinting; when using a 3D printer it is possible to produce tissues, human organs, or special products that include living cells. A certain impetus in the development of bioprinting can be explained by successful experiments with induced pluripotent stem cells (iPS) and multipotent stem cells, which can be used to differentiate cells of various adult patient lines (Volkova & Ermakov, 2016:257). This solves a significant number of ethical issues, since early experiments were carried out with embryonic stem cells (ESCs), leading to the death of the embryo. In addition, the main source of ESCs is aborted material, which caused serious discussions about the beginning of life and the dignity of nasciturus (unborn). But even this aspect of using additive technologies in biomedicine is far from being the only one. In 2016,

[1]3D-printed EDAG Light Cocoon concept car arrives in Geneva. Available at: http://www.autode.net/news/EDAG_Light_Cocoon [Accessed 10th June 2022].
[2] Chepur A. Cars printed by a printer. Available at: https://www.computerra.ru/241280/avtomobili-napechatannye-na-printere/ [Accessed 10th June 2022].
[3] Aleksandrov D., Sergeeva D. From shelters to palaces: ten buildings printed on a 3D printer / the RBC group. Available at: https://trends.rbc.ru/trends/innovation/60f5ad5f9a7947a81f1e63cf [Accessed 10th June 2022].

4D (four-dimensional) printing based on stereolithography was first introduced in biomedicine, making neural engineering possible (Miao, et al., 2018).

Economic indicators of 3D bioprinting are also impressive: in 2020, the global market was valued at $724.17 million. In 2026, it is forecasted at the level of 2398.27 million US dollars. The average annual growth rate is 21.91%. The fastest growing market is the Asia-Pacific region (China, Japan, Singapore, and South Korea being the leaders)[4].

Strategies for the Development of Additive Technologies and their Regulatory Framework

The spread of additive technologies contributes to:

— decentralizing production (there is no need to create large production capacities and concentrate human and other resources) (Ben-Ner & Siemsen, 2017);

— improving production efficiency and reducing waste (which largely provides support from environmental human rights organizations) (Ahn, 2016);

— reducing the time of developing and introducing them into mass production with a simultaneous increase in the quality of the finished product (Mies, Marsden & Warde, 2016:114—142);

— expanding the population's access to material goods (additive technologies reduce the cost of production, allowing the creation of various objects of the material world practically at home) (Chen, et al., 2017:3652);

— minimizing state control and the absence of strict regulatory documents (which only accelerates the spread of technology and further experimentation) (Calderaro, Lacerda & Veit, 2020).

Such trends lead to the fact that many states (or on their behalf and with the support of non-governmental organizations) are constructing development strategies. So, back in the early 1990s, in Sweden, a group of scientists presented the Framework for Strategic Sustainable Development (FSSD), which is occasionally reviewed and supplemented. Starting in 2015, additive technologies have been given increasing importance in this document (Villamil, et al., 2018:1384).

In the UK, the National Center for Additive Technologies, which proposed its own Strategy[5], was created. Before that, the initiative to form a policy document came from business structures, which, due to active promotion by researchers from the University of Nottingham and Cambridge, formed a working group, held seminars, created a website for proposals (as a result, about 150 interested organizations have

[4] 3D Bioprinting Market — Growth, Trends, COVID-19 Impact, and Forecasts (2021—2026). Available at: https://www.reportlinker.com/p06079791/3D-Bioprinting-Market-Growth-Trends-COVID-19-Impact-and-Forecasts.html?utm_source=PRN [Accessed 10th June 2022].

[5] Additive Manufacturing National Strategy for the UK. Available at: https://hvm.catapult.org.uk/news/an-additive-manufacturing-national-strategy-sets-out-to-establish-the-uk-as-a-world-leader/ [Accessed 10th June 2022].

submitted their recommendations for two years), and held consultations with industry communities of entrepreneurs (Minshall & Featherston, 2019). Consequently, 12 trends for developing additive technologies have been designed (they are not related to industry regulation, but to allocating the so-called *points of activity*[6]). Austria followed suit, where the Roadmap for the Development of Additive Technologies was adopted, and the specially created Association for the Promotion of Additive Manufacturing[7] was designated as the main engine of ideas.

In India, the National Strategy for Additive Manufacturing has been developed by the Ministry of Electronics and Information Technology (its draft was published in December 2020 and approved in June 2021)[8] . At the forefront were set such goals as developing their own additive industry, strengthening international cooperation (including by localizing the production of world leaders), promoting innovation and research infrastructure, stimulating manufacturers, etc. Particular attention is paid to the use of technologies in biomedicine, it is emphasized that this will lead to reducing healthcare costs, rapid response in case of emergencies, personalizing treatment and selecting medicines.

In China, an Inter-Agency Plan to Support the Development of the Additive Manufacturing Industry has been developed[9]. In the United Arab Emirates, additive technologies have become an element in the transition to industry 4.0 in partnership with Siemens[10]. In fact, a similar approach to forming a general strategy for developing 4.0 industry is typical for many European countries, where additive technologies are designated among the breakthrough areas.

In Russia, the Decree of the Government of the Russian Federation No. 1913-r of July 14, 2021, approved the Strategy for the Development of Additive Technologies in the Russian Federation for the period up to 2030, which should be recognized as a significant factor, given the speed of development of additive technologies and the prospects for their implementation in various sectors of the Russian economy. However, the given figures on the economic effect of their implementation still look very modest in comparison with the countries cited above. The world experience indicates a 30% growth in this industry, which creates prospects for the Russian industry as well. Moreover, the Strategy does not indicate the gaps in the Russian legislation, which are outlined in foreign documents. There

[6] Among them: the development of additive technologies for small and medium-sized businesses; formation of requirements for professional skills and abilities; expert group support; raising awareness of new technologies, etc.

[7] Additive Manufacturing Austria (AM Austria). Available at: https://produktionderzukunft.at/en/platforms/additive-manufacturing-austria.php [Accessed 10th June 2022].

[8] National Strategy on Additive manufacturing (AM). Available at: https://www.meity.gov.in/writereaddata/files/National%20Strategy%20for%20Additive%20Manufacturing.pdf [Accessed 10th June 2022].

[9] Website of the Government of the People's Republic of China. Available at: http://www.gov.cn/xinwen/2017-12/14/content_5246754.htm [Accessed 10th June 2022].

[10] Mansoor Z. UAE's Ministry of Industry and Advanced Technology, Siemens partner to underpin digital transformation. Available at: https://gulfbusiness.com/uaes-ministry-of-industry-and-advanced-technology-siemens-partner-to-underpin-digital-transformation/ [Accessed 10th June 2022].

are no special clarifications on the prospects of bioprinting. One can only refer to the distribution of the share of consumers of additive technologies, where, according to the Strategy, medicine takes 11%.

The lack of regulations governing the use of 3D printing has led to radical proposals, supported by some facts that have become known. In 2012—2013 in the United States, the Defense Distributed group announced the creation of a gun with the help of new technology. At the same time, special drawings were posted on the Internet so that everyone could take advantage of their achievement. This led a number of states to come up with a legislative initiative to completely ban additive technologies (later they adopted the amendment to ban printing of weapons), but it did not find the necessary support[11]. In January 2022, the Sheffield Crown Court took on a case of "fascist terror cell" which had created a special chat room for spreading radical right ideas and trying to supply their supporters with weapons using 3D printing. To do this, they searched for drawings on the Internet and purchased a special printer[12].

Main Areas of Development of Bioprinting and Challenges of their Legal Support

Bioprinting (as one of the areas of additive technologies) is increasingly demonstrating certain achievements that carry a significant potential for new discoveries and approaches in treating certain diseases. Initially, as part of regenerative medicine development, there were attempts to layer cellular material (of organic or neutral inorganic nature) onto a frame. This technology has gained some notoriety due to the extraordinary activities of a very controversial personality — Paolo Macchiarini. As a professor at Karolinska University (Stockholm, Sweden) he tested the transplantation of an artificial trachea formed from the cells of the patient (so called *tissue engineering method*). A successful experiment was announced in 2008; in 2011 the related article was published in The Lancet journal. In 2014, based on a five-year follow-up, the Lancet journal mentioned a breakthrough and improvement in the quality of life of the patient at the Clinic of Thoracic Surgery of the University of Barcelona (Gonfiotti, et al., 2014). However, the Macchiarini team's conclusions were refuted (Molins, 2019:1099), and the 2011 article was retracted due to violations of ethical and scientific research principles[13]. Interestingly, P. Macchiarini was a visiting professor at the Kuban State Medical University

[11] Morelle R. Working gun made with 3D printer. BBC news. 2013. 6 May. Available at: https://www.bbc.com/news/science-environment-22421185 [Accessed 10th June 2022].

[12] Dearden L. Extreme fascist terror cell» recruited children while making explosives and 3D-printed gun, court hears. The Independent. 2022. 21 Jan. Available at: https://www.independent.co.uk/news/uk/crime/far-right-terror-cell-3d-guns-b1997185.html [Accessed 10th June 2022].

[13] Retraction — Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. The Lancet. 2018. Vol. 392. № 10141. P. 11. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31558-7/fulltext [Accessed 10th June 2022].

(Krasnodar), where he participated in implementing a mega-grant from the Russian Government. But even there, the surgery performed according to his method was not successful. Yet, the very idea of creating a three-dimensional transplant is not denied, and it is bioprinting that inspires hope for its successful implementation (Damiano, et al., 2021).

Thus, significant prospects in 3D printing are seen in creating human organs and tissues. There are successful cases of a human ear bioprinting (e.g., in Australia and the USA[14]). Bioprinting of cartilage tissues is also rapidly developing (Arguchinskaya, et al., 2021) along with skin bioprinting (taking into account the prevalence of its damage — from burns to various wounds and ulcers). In the latter case, bioprinting is possible in various forms for subsequent transplantation (including the use of artificial materials), as well as skin bioprinting *in situ*, that is, on the spot. In this case, a specially designed printer "prints" skin cells directly into the injured wound, "delivering dermal fibroblasts and epidermal keratinocytes to specific wound parts, reproducing the layered structure of the skin and accelerating the formation of normal skin structure and functions" (Albanna, et al., 2019). Bioprinting also allows skin printing while preserving the vascular network, as well as the function of pigmentation, reconstructing hair follicles, and developing sweat glands. However, there are some difficulties with regenerating the nervous system to maintain the sensitivity of the restored area (Weng, et al., 2021:1—28). In the Russian Federation, the lag in the technology development is largely due to the lack of special 3D printers, but there are successful projects here too. So, in May 2021, a printer for printing human tissues (potentially organs as well)[15] was presented at St. Petersburg State University.

Bioprinting of organs is a promising area. Organ deficiency is a worldwide problem. The mortality rate while waiting for an organ transplant in 2020 ranged from 1.8% (for a donor kidney) to 7.5% (for a donor heart). Coronavirus infection made its own adjustments; 2020 demonstrated a drop in the number of *effective donors*, although in general, transplantology in Russia did not suffer significant losses (Gautier & Khomyakov, 2021). Given such imperative, the solution to the main issue — the lack of donor organs — is sought in various areas with bioprinting occupying its specific place. In the spring of 2019, scientists at Tel Aviv University printed a three-dimensional heart (it is small in size, but with blood vessels, ventricles and chambers)[16]. In Russia, attempts have been made to bioprint the thyroid gland (Khesuani,[17] 2020:186). Even though the prospects

[14] Hitti N. University of Wollongong uses stem cells to 3D-print human ears. Available at: https://www.dezeen.com/2019/03/25/3d-printing-human-ears-university-of-wollongong/ [Accessed 10th June 2022].

[15] Aprinterfor 3D-printing of human tissues has been developed in St. Petersburg. Available at: https://nauka.tass.ru/nauka/11438111 [Accessed 10th June 2022].

[16] Efrati I. Israeli Scientists Print World's First 3-D Heart. Available at: https://www.haaretz.com/science-and-health/.premium-israeli-scientists-print-world-s-first-3-d-heart-1.7124321 [Accessed 10th June 2022].

[17] Yu. Khesuani is Executive Director of the 3D Bioprinting Solutions laboratory, which, together with INVITRO and Roscosmos, is the most active in Russia in the field of bioprinting research.

are being built, the real appearance of such full-fledged organs is still forecasted for the distant future. However, even now bioprinting of organs has its specific application.

First of all, it is connected with the surgical planning. The complexity of some surgical operations requires careful preparation. Modeling has already been tested in surgeries on the heart (Yang, et al., 2015:300), liver (Zein, et al., 2013:1305), kidney (Tejo-Otero, Buj-Corral & Fenollosa-Artés, 2020:537). In fact, surgeons from the Kobe University Hospital (Japan) routinely use 3D models to plan liver transplantation. Copies of the patient's organs serve as a testing ground for planning the removal of a part of the donor liver with minimal tissue loss and maximum compliance with the recipient's abdominal cavity (Ventola, 2014:704—711).

Secondly, the printed organs are used for conducting experiments on them and studying the reaction to the impact of a particular substance. Thus, scientists from Nano3D Biosciences and Houston Research Institute developed a three-dimensional model of the breast to simulate heterogeneous tumors, which allowed to model the effect of the tumor microenvironment on drug effectiveness (Jaganathan, et al., 2014). Such alliances between manufacturers of bioprinters and research institutions result in certain success. In early 2021, as part of the European ENLIGHT project, Readily3D[18], a Swiss bioprinter manufacturer, pooled efforts with the leading academic centers and companies across Europe to develop a living model of the pancreas to improve diabetes drug testing (the European Horizon 2020 programme which envisages the allocation of billions of dollars for the development of breakthrough scientific technologies)[19].

A separate area is bioprinting of implants. In 2012, an 83-year-old Belgian became the first person to receive a 3D-printed jawbone (from titanium powder which was heated and laser-fused)[20] made specifically for her face using a 3D-printer. Implants created in this way are made specifically for the needs of a particular patient (with configuration detailing, departing from the standard sizes used in industrial production) (Javaid & Haleem, 2018). Thus, bioprinting seems to be very prospective in orthopedics and prosthetics. In dentistry, leading companies use additive technologies to manufacture unique bracket systems. For instance, Invisalign produces about 50,000 removable orthodontic braces daily[21].

The above-mentioned success in the development of additive technologies lead to adjustment of health legislation, which so far has not taken into account the novelties of the progress. Thus, it is essential to introduce a general regulation on

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[18] Readily3D. Available at: https://readily3d.com/ [Accessed 10th June 2022].

[19] Anusci V. Readily3D’s volumetric bioprinters will make pancreatic tissue for ENLIGHT project. Available at: https://www.3dprintingmedia.network/readily3ds-volumetric-bioprinters-will-make-pancreatic-tissue-for-enlight-project/ [Accessed 10th June 2022].

[20] Moscaritolo A. Woman Receives 3D Printer-Created Transplant Jaw. Available at: https://in.pcmag.com/printers/88979/woman-receives-3d-printer-created-transplant-jaw [Accessed 10th June 2022].

[21] Invisalign Available at: https://www.invisalign.com/ [Accessed 10th June 2022].

bioprinting into Article 47 of the Federal Law No. 323-FZ of November 21, 2011 On the Fundamentals of Health Protection of Citizens in the Russian Federation dedicated to the donation of human organs and tissues and their transplantation. Detailed clarifications are required for the Law No. 4180-1 of December 22, 1992 On Transplantation of Human Organs and (or) Tissues, namely:

— establishing admissibility of bioprinting of human organs and tissues for their subsequent transplantation, as well as the concept of a human organ and tissue produced with additive manufacturing technologies (it can formally fall under the concept of a medical device that has its own normative consolidation, but hardly reflects the intended purpose of the newly created organ);

— determining special requirements for organizations that carry out bioprinting of human organs and tissues, for printers for printing human organs and tissues, for "bio-ink", as well as for specialists in the field of additive technologies used in biomedicine;

— changing the procedure for obtaining the recipient's consent specifically for the printed organ, and not for the one provided by the donor (variability of "bio-ink" suggests variants of the consent content);

— liberalizing the circulation of human organs and tissues manufactured with the help of additive technologies (rejection of the absolute principle of inadmissibility of the sale of human organs and (or) tissues, provided for in Article 15 of the Law On Transplantation of Human Organs and (or) Tissues).

It is necessary to expand the regulatory powers of the Ministry of Health of the Russian Federation (in terms of adopting by-laws) and, apparently, Roszdravnadzor (in terms of exercising control functions). Introduction of certain standards will be required for all stages of the bioprinting process: from the development of the future organ (tissue) model, choice of "bio-ink" and bioprinting method to the bioprinting process itself (with checking the print layer, individual parts of the organ (tissue)), printing accuracy, evaluating the conformity of the finished product to the approved standards and its biocompatibility, and post-implantation functionality. As most writers in the field of bioprinting note, "The ideal workflow of bioprinting should start from retrieving patient-specific cells through biopsy, designing the morphology of the organ or tissue to be replaced, and going back to the patient at the end for the transplantation of a functional organ" (Santoni, et al., 2022:14—42).

In a number of countries, it is proposed to extend the legal regime of a biomedical cell product to tissues created using additive technologies (Derakhshanfara et al., 2018: 149). However, there is no consensus on this model of regulation, it is still under discussion. If we take this path, then we should take into account the Federal Law No. 180-FZ of June 23, 2016 On Biomedical Cellular Products, which provides for a fairly bureaucratic procedure of BCP registering and its launching into the market (Posulikhina, 2020:163). Moreover, many standard procedures that are typical of drugs and BCP will not be applicable to human organs and tissues created through bioprinting.

The introduction of bioprinting into clinical practice will require amendments to the Procedures and Standards for the provision of medical services, as well as to the relevant clinical recommendations (this is related to Article 37 of the Federal Law On the Fundamentals of Health Protection of Citizens in the Russian Federation). Besides, additive technologies at the current stage of development are not financially affordable for a Russian citizen, which leads to the adoption of a target platform that provides both economic incentives for their implementation and their inclusion in the program of state guarantees for free medical care to citizens.

It is also necessary to take into account organizational and legal issues, starting with the concept of institutional readiness, i.e., the ability of the entire Russian healthcare system to use additive technologies properly. The new industry will require significant financial resources, which can be obtained through public-private partnerships and interest from commercial organizations. Given the leadership of some countries in this technology, the requirements for institutional readiness in setting priorities can be decisive in the scale of potential investors' values. These requirements should include various parameters: from training of specialists to ethical assessment of the applied results of bioprinting. Appropriate logistics should be established (Varkey, et al., 2019); this requires more amendments to the Russian legislation. For example, the production of bio-inks will require collection of donor cellular material (Lowdell & Thomas, 2017), which in turn will lead to clarifications to the above-mentioned Law on Biomedical Cell Products and the Federal Law No. 125-FZ of July 20, 2012, On Donorship of Blood and its Components.

Biomedicine, intruding the sensitive sphere of the personal essence, is significantly influenced by ethical documents formed by various non-governmental organizations with the World Medical Association (WMA) playing a significant role. Under its auspices, the basic documents have been adopted: the International Code of Medical Ethics (adopted in 1949, supplemented in August 1968 and October 1983), the Declaration on Human Organ Transplantation of (Madrid, October 1987), the Resolution on Physicians' Conduct Concerning Human Organ Transplantation (Stockholm, September 1994). It is easy to assume that in the near future the WMA will face the task of adopting a common document on the legal limits of additive technologies. Apparently, the main problems could be solved in such a declaration. However, such a document (with all the breadth of the possible subject) will not be of decisive importance (it will rather be aimed at ascertaining directions for development). Practice shows that ethical regulation to a greater extent began to acquire the character of a quick response to an emerging problem; it is achieved through the functioning of permanent bodies on bioethics. This approach seems to be the most promising.

Foreign experience shows that the functions of developing ethical recommendations in the event of disputable situations are assigned to ethical committees (or ethics councils), professional corporations of medical workers, and various specialized organizations authorized for ethical examination and giving opinions. The framework nature of many ethical documents, designed not to detail each step of the researcher, but to outline the general boundaries of ethical behavior also contributes to the issue.

The European model of developing ethical principles for the activities of medical professionals and their subsequent application is based on the self-regulatory public corporation that unites doctors by prescribed membership. For example, in France, there is the Code of Ethics for Occupational Health Professional adopted by the Order of the Physicians of France[22]. The structure of a unified professional association of medical workers in Western Europe always provides for the creation of a body responsible for interpreting (giving clarifications) on complex ethical issues. The website of organizations, as a rule, can deal with individual cases with detailed ethical and legal characteristics. A similar model is being actively discussed in the professional Russian community (on the basis of the National Medical Chamber, headed by famous doctor Leonid Roshal). It is within the framework of this approach that the bioethics of additive technologies should be formed.

The use of additive technologies in the production of medical devices will lead to amending Article 38 of the Law On the Fundamentals of Health Protection of Citizens in the Russian Federation. The properties of the final medical product may depend on many factors, including disposability/reusability, ability to withstand a certain load, manufacturing according to standard sizes or individually according to the patient's parameters. All this imposes additional regulatory powers on the state authorities (control over the technological process, content of the digital file, quality of the material or the final product, and/or its post-processing). Also, the spread of bioprinting may bring to decentralization of the industrial process. Different countries open up new opportunities by publishing freely available technological documentation for producing certain products. Thus, in the United States, the National Institutes of Health (responsible for distributing budgetary funds for further development of medicine) has created a special website with open access to formulas, schemes, and source code for various bioproducts (including replicas of proteins, viruses, and bacteria) that can be printed on a bioprinter[23]. This approach is designed to popularize additive technologies and promote them. In the Russian Federation, the well-known medical company INVITRO has created a 3D Bioprinting Solutions laboratory, which actively promotes bioprinting, using close cooperation with the State Corporation Roscosmos and the Skolkovo Foundation[24]. Apparently, the experience of the laboratory could be used when giving it a special status of coordinator of relevant research and/or developer of draft regulations and technical

[22] Le code de déontologie. Available at: https://www.conseil-national.medecin.fr/code-deontologie [Accessed 10th June 2022].
[23] NIH 3DPrintExchange. Available at: https://3dprint.nih.gov/ [Accessed 10th June 2022].
[24] Russia was the first in the world to print living tissues in space. Available at: https://www.roscosmos.ru/25849/ [Accessed 10th June 2022].

requirements for the bioprinting process itself. It is important to emphasize that introduction of additive technologies will lead to the adoption of a significant number of clarifications of a technical nature, which should be developed by the participants in such production.

Law, Bioprinting and Biopharmaceutics

Additive technologies have found their application in testing medicines. 3D printing creates small organ-like structures (they are called organoids) on which experiments can be carried out for screening pharmaceuticals. Until recently, the classical model was based on the two-dimensional use of cell cultures, which preceded animal experiments. However, in this case, as researchers note, they often faced a methodological gap. 3D printing allows creating the necessary organoid (including with the pathological process) and conducting the necessary experiment *in vitro*, which, in its turn, allows simulating molecular and cellular mechanisms, identifying intercellular interaction, determining biophysical parameters (such as bioavailability of drugs and features of their delivery to various cell populations). Organoids help to imitate the pathophysiological condition (with a detailed repetition of the natural complexity and clinical significance).

Modulation of targets on animals also suffers from a number of disadvantages. A human being demonstrates serious interspecies differences with representatives of the animal world (although there may be coincidences in a number of features, and minimal genetic differences with some animals). This causes different reactions of the body when using drugs (Peng, et al., 2017:26—46). Moreover, the use of animals as objects of experiments encounters more and more serious ethical difficulties. The reference to Western legal doctrine points to the formation of an integral concept of “*non-human rights”*. The additional term *jus animale* (animal rights) is also used; it takes the issue beyond the protection of objects of the animal world. In fact, the first scholar who publicly announced the new system of law was a representative of pre-revolutionary Russian legal science — N.N. Shulgovsky. The author specifically pointed out that this approach suggests talking about recognition of possible *rights* for animals as for a human person (Shulgovsky, 1906:60).

The American company Organovo has developed an exVive3D liver tissue model capable of “providing more accurate predictors of hepatotoxicity in the early stages of research” (Vaidya, 2015). The design of the course of tumor processes in oncological diseases has become a common method (Zietarska, 2007:872—885). It allows testing chemotherapy drugs, determining the response of the tumor, thereby personalizing the dosage. The production of tissues and organs with certain pathologies for subsequent testing of drugs is pushing the entire healthcare system to expand a personalized approach to selecting the most effective dose for a particular patient (predictive drug screening) (Mazzocchi, Votanopoulos & Skardal, 2018:97—104).

The main areas of development of additive technologies in biopharmaceuticals are:

— modelling of human organs for drug response experiment, i.e., preclinical studies;

— phenotypic screening, i.e., determining the necessary combination of drugs while determining the method of treatment (in relation to an indefinite range to clarify clinical recommendations);

— toxicogenomics, i.e., studying the toxicity of drugs in individual selection (widely used with various diseases, while monitoring not only the effect on the treatment process, but also toxicity to other organs in order to minimize side effects);

— 3D skin modelling for testing cosmetological products, which allows to abandon animal experiments most severely criticized by animal rights activists. If in the situation with medicines it is still possible to make allowance for saving a person's life, cosmetology in most cases is not aimed at providing specific medical care.

With individual selection, bioprinting of several organs is also possible; this allows to model the entire complex of effects of drug intervention complimenting beneficial advantages of the technology.

Speaking about Russian modern GOSTs/ISO we can assert that they do not consider the possibilities of bioprinting. For example, "GOST ISO 10993-3-2018. Medical devices. Assessment of the biological effect of medical devices. Studies of genotoxicity, carcinogenicity and reproductive toxicity" and "GOST ISO 10993-1-2021. Medical devices. Assessment of the biological effect of medical devices. Part 1. Evaluation and research in the process of risk management" mention transgenic animals (one of the methods for creating animals that include separate human parts of DN) but say nothing about additive technologies.

With the help of additive technologies, it is also possible to manufacture medicines. Currently, the only 3D printed drug product is Spiritam (levetiracetam which is used to treat partial epileptic seizures)[25]. It received its official approval in 2015 in the USA, but without identifying a method of production as part of the standard registration procedure.

Bioprinting can improve pharmaceutical manufacturing by printing precise individual drug dosages on the spot, as well as producing complex profiles. It is assumed that this will give an additional impetus to the development of personalized medicine. The patient will not buy standard mass-produced pills but will address pharmacy with a ready-made formula prepared by the attending physician, which might be the basis for printing a complex pill for oral use (as the most popular dosage form). Special scientific literature highlights that oral pills are currently prepared by well-established processes such as mixing, milling, and dry and wet granulation of powdered ingredients, which are formed into tablets by compression or moulding. Each of these manufacturing steps can introduce difficulties, such as drug degradation and form

[25] Spiritam. Available at: https://www.spritam.com/#/patient [Accessed 10th June 2022].

change, possibly leading to problems with formulation or batch failures (Okafor-Muo, Hassanin, Kayyali & ElShaer, 2020). In addition, complex drugs require different release profiles (including delayed release) of drugs and therapeutic parameters. 3D printing gives an opportunity to avoid these negative nuances by creating pills with complex geometry, layers or multi-level shells (Li, et al., 2021). Thus, the attending physician, collecting an anamnesis, determines the pharmacogenetic profile of the patient, as well as their various characteristics (gender, age, weight, other characteristics), decides on the optimal doses of drugs and their combination. On this basis, the necessary formula is formed, which is presented to the pharmacist for individual printing on a 3D printer.

Bioprinting of drugs has significant differences from the already existing production of some drugs in modern pharmacies. Bioprinting involves the decentralization of industrial production, which creates completely different risks. Apparently, their understanding causes a wary attitude towards additive technologies in pharmaceuticals on the part of regulators in various countries. Spiritam is practically the only drug that has received state registration. The fight against counterfeiting in this industry occupies a large amount of work of public bodies, where various models of counteraction are offered (from total control checks to special labeling and the introduction of a state monopoly). The spread of 3D printing can destroy all established traditional mechanisms. In addition, the pharmaceutical companies themselves have not yet decided on the cost-effectiveness of drugs created with new technology. That is why any innovations will give rise to serious scientific discussions.

The development of bioprinting in the pharmaceutical industry will lead to an update of the regulatory framework, namely, amendment of the Federal Law No. 61-FZ of April 12, 2010 On Medicines Circulation, as well as the Federal Law On Biomedical Cell Products. At the same time, it will be necessary to provide for an independent procedure for registering drugs newly created and manufactured using bioprinting, as well as a procedure for registering already created drugs on a different production platform. In this part, it is necessary to update the regulatory mechanism by assigning additional functions to the Russian Ministry of Health and Roszdravnadzor. To say the least, it is necessary:

— to introduce a licensing mechanism for the process of bioprinting of organs used in pharmaceuticals;

— to introduce requirements for the process of conducting experiments on organs manufactured by bioprinting;

— to establish regulations for considering applications for approval of medicinal products that have been tested on organs produced by bioprinting.

Conclusion

All over the world, the potential for developing additive technologies is highly appreciated, biomedicine occupying a special place (since it is in this area that they can directly affect human life and health). The vast majority of developed countries adopt strategic documents aimed at introducing innovations into common practice. At the same time, many of the risks that emerge as a result of new discoveries in biomedicine are enhanced when they are combined with the threats posed by bioprinting. The example above concerned using 3D printing to produce weapons. Extensive publicity to such examples led to attempts to totally ban the entire technology. Establishing a ban is the easiest way, but will it be correct and will it correlate with the long-term plans of science, state and society? — this is a rhetorical question.

In a number of countries, it is proposed to introduce universal registration of 3D printers. The Russian Federation went through something similar, when in 1994 (Decree of the Government of the Russian Federation No. 1158 of October 11, 1994 Procedure for the Registration, Storage and Use of Color Copying Means in the Russian Federation), rules for registering color copying media were introduced. At that time, it related to the fight against counterfeit currency. In 2010, this document became invalid, but until that time it had been practically ignored by all participants in relations (from citizens and legal entities that purchased such equipment to the Ministry of Internal Affairs bodies authorized to register equipment).

For the time being, a bioprinting 3D printer is not very cheap, but it can be purchased for profit (personal use is hardly possible in the nearest future); then decentralization and personalization of production may threaten industrial volumes. In this case, the risk of infringement of patent holders' rights is rather high. And there are no unambiguous ways for improving legislation. Now states are interested in promoting additive technologies, which is ensured, among other things, by *exposure* of some industrial secrets. At the next stage, apparently, the priorities will shift in another direction. At the same time, it will be possible to use bioprinting based on cheap, low-quality bio-inks, as well as outright fakes. Strengthening of regulatory functions can lead to a slowdown in progress, which is why in many countries the administrative burden on participants in such a biomarket is still being minimized. Moreover, the legislator will need to solve a basic problem: extending the general terminology of 3D printing to the biomedical field. This suggests adoption of the Federal Law On Additive Technologies or using a *sui generis* categorical apparatus for created products. But even if the second model is adopted, the variability is possible: adoption of point changes in laws in the field of healthcare and medicines circulation, or only a general directive in the Federal Law On the Fundamentals of Health Protection of Citizens in the Russian Federation with the adoption of a separate by-law for each individual case. In case of the latter option, there is a danger of *drowning* in administrative rulemaking. Let us add that constant progress will multiply new products, which will not bring legal certainty.

We must not forget that each stage of the bioprinting development creates additional bioethical problems that need to be understood and discussed publicly. In fact, both patient's own cells (autologous) and donor's cells (allogeneic) can serve as the basis for bio-ink. In some cases, it is possible to use only donor material due to the rejection of the patient's own cells by the body. But here all the same questions arise related to sampling cells and tissues that were known even before the development of bioprinting. Judicial practice already knows many examples when cellular material was gathered with various violations. Any such stories that get public coverage arouse demands for effective inspection, which, in turn, creates administrative barriers. Accordingly, it is essential to clearly consider the scope of supervisory functions and powers of regulatory bodies, so as not to destroy the growing technology.

It is also necessary to consider a system of exceptions when establishing bioprinting in medical organizations in case there is a ban on the transfer of devices to other organizations and/or incompliance with the standards for producing and using bioprinters for the target group of patients. A similar approach is being tested in Western European countries, where a somewhat universal *Hospital Exemption* approach is allied (a pharmaceutical exception for medical organizations that allows them to use an advanced therapy drug without centralized registration, if it is used in the organization where it was produced for a specific patient). Such model has been successfully tested on biomedical cell products thus accelerating their implementation in clinical practice. In Japan, in 2013, a special law has been adopted (Act No. 85 of November 27, 2013 On the Safety of Regenerative Medicine[26]) which covers "cell therapy, the safety and efficacy of which have not been established", including: (1) technologies designed to reconstruct, restore, or shape the structure or functions of the human body; (2) technologies designed to treat or prevent human diseases using processed cells. Article 243 of the Code of the Republic of Kazakhstan No. 360-VI ZRK[27] of July 7, 2020 On the Health of the People and the Healthcare System establishes the procedure for using advanced therapy medicines, which can also be extended to bioprinting.

It is not of the results of activities in medical organizations that the greatest risks are expected, but of the consequences of total decentralization of production, when a bioprinter can practically be purchased by any citizen for home use. 3D printing is changing the established scheme for manufacturing medicines and medical devices, altering the entire chain from the initial stage (bio-ink production) to providing it to the end user. From there, it may be asserted that bioprinting can fit into the established framework of regulatory control, while respecting the boundaries of its usage. The threat comes only from specific aspects of 3D printing, namely, from the potential of decentralized production.

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[26]Act on the Safety of. Regenerative Medicine. Available at: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000150542_00001.html [Accessed 10th June 2022].

[27] Code of the Republic of Kazakhstan No. 360-VI ZRK of July 7, 2020 On the Health of the People and the Healthcare System. Available at:https://online.zakon.kz/Document/?doc_id=34464437 [Accessed 10th June 2022].

Thus, bioprinting is increasing its relevance, offering solutions to issues that are essential for modern medicine. The rapid spread of this technology urges the need for its legal regulation. Even now, correction of the basic acts is required; it must consider the real results of 3D printing. The most optimal is the risk-based approach, which causes intervention of the regulator only where there are significant threats to the security of the individual, society and the state. This imposes a special responsibility on the domestic regulator (represented by the Ministry of Health of Russia and Roszdravnadzor), which is obliged to find the happy middle ground between administrative control and freedom of scientific research.

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