
Science and Society

Safe Use of Genetic Technologies

M. P. Kirpichnikov^{a,*} and A. M. Kudryavtsev^{b,**,#}

^a Moscow State University, Moscow, Russia

^b Vavilov Institute of General Genetics, Russian Academy of Sciences, Moscow, Russia

*e-mail: kirpichnikov@inbox.ru

**e-mail: kudryav@vigg.ru

Received January 24, 2022; revised January 27, 2022; accepted February 5, 2022

Abstract—The prospects and problems of the development of modern genetic technologies are analyzed, and pressing issues of updating the regulatory framework for the safe use of their products are posed in this article, which is based on the materials of reports at the RAS Presidium meeting on December 7, 2021. At the end of 2018, by Presidential Decree no. 680 On the Development of Genetic Technologies in the Russian Federation, this R&D area was declared a priority. According to the authors, to expand genetic technologies in Russia, it is necessary to change the concept of their legal regulation and to bring the legislative norms in line with the current level of the development of science in this area, including the adjustment of the genetic engineering nomenclature.

Keywords: biosafety, genetic engineering, genome editing, GMOs, legal regulation, Russia

DOI: 10.1134/S1019331622030029

The formation of a new technological order, in which the leading role is assigned to innovative genetic technologies (GTs), has become the basis of world socioeconomic development. Undoubtedly, along with information technologies and nuclear energy, GTs are strategically important and serve as the most important tool in advancing science, medicine, industry, and agriculture and in solving the problems of sustainable development, national security, and the improvement of the quality of life in general. In Russia, the priority of genetic technologies has been repeatedly noted, in particular, in the Presidential Decrees of November 28, 2018, no. 680 (On the Development of Genetic Technologies in the Russian Federation [1]) and of July 21, 2016, no. 350 (On Measures to Implement State Scientific and Technological Policy in the Interests of the Development of Agriculture [2]). The use of GTs in pharmaceuticals is covered by Federal Law no. 61-FZ On the Circulation of Medicines (2010). The procedure for the circulation of biomedical cell products is fixed in Federal Law no. 180-FZ On Biomedical Cell Products (2016). State interest in genetic technologies was also shown during the formation of the state program of the Russian Federation for 2019–2030 Scientific and Technological Develop-

ment of the Russian Federation (Resolution of the Government of the Russian Federation no. 377 of March 29, 2019).

Status and problems of the development of genetic technologies in Russia. Genetic technologies are in demand all over the world in various fields of practical activity and occupy top positions in the basic research ranking. Effective genetically engineered drugs are already widely and successfully used in Russian health care and pharmaceuticals. Using GTs, a number of protein preparations have been obtained, including interferons, blood coagulation factors, and hormones (for example, insulin), as well as vaccine preparations and antibiotics. Also note the success in the treatment of a number of socially significant diseases (oncological and infectious) using therapeutic antibodies, obtained with the help of genetic technologies.

Advanced systems for editing the human genome, which, obviously, will be used in clinical practice in the near future, should also be attributed to new gene therapy approaches. This refers to genome editing of somatic cells that does not affect the genome of human germ cells. The recombinant vaccines against Ebola and the new coronavirus infection SARS-COVID-19 during the pandemic have become a colossal achievement of Russian genetic engineering and GT. Such drugs are both immunobiological and gene therapeutic.

The Federal Scientific and Technical Program for the Development of Genetic Technologies for 2019–2027, approved by a resolution of the Russian govern-

[#] RAS Academician Mikhail Petrovich Kirpichnikov is Academician-Secretary of the RAS Division of Biological Sciences and Dean of the Faculty of Biology of Moscow State University. RAS Corresponding Member Aleksandr Mikhailovich Kudryavtsev is Director of the Vavilov Institute of General Genetics, RAS (VIGG RAS).

ment (no. 479, 2019), provides for the use of genome editing systems in the agroindustrial sector. It is planned to create at least 30 lineages of agricultural plants and animals with accelerated access to varieties and breeds, including aquaculture.

Back in the early 1990s, studies of prominent Soviet (Russian) geneticists and molecular biologists formed a large groundwork in the genetic engineering of plants; animals; strains of industrial microorganisms; and models of plant recombinant vaccines for use in the real sector of the economy, including in the agroindustrial complex. We mean the works of Academicians I.G. Atabekov [3], K.G. Scryabin [4, 5], V.G. Debabov [6], L.K. Ernst [7], and others. However, due to certain peculiarities of the domestic legislation regulating the use of genetically engineered organisms, these studies remained within the walls of laboratories and were not used to increase the productivity of agricultural objects and their resistance to natural and anthropogenic factors, while genetically modified agricultural products of foreign companies ended up in turnover in the Russian market. At the same time, the opportunity was missed to transfer scientific selection to new technological tracks in the shortest possible time by combining the efforts of breeders and geneticists.

Of course, the wary attitude of the public to genetically modified organisms contributed to the prohibitive measures in the legislation. However, over the many years of using GMOs in foreign agriculture, no direct negative effect of these organisms on human health has been identified. Moreover, over the last decade, Russian geneticists have convincingly shown that GMOs can be obtained not only in the laboratory but also spontaneously, in the wild. Natural GMOs include crops such as peanuts, hops, cranberries, sweet potatoes, tea, etc. [8]. Many of the natural transgenic species have been used for food and medicine throughout human history without any adverse effects. The process of the emergence of new GMOs in nature is continuous.

Today, Russia has begun research using new GTs in breeding, including genome editing, and a number of striking results have already been obtained, in particular, in world-class Russian genomic centers. Examples of targeted crop editing include the following:

- A shift in the earing time of common wheat (in accordance with concrete climatic conditions) (the All-Russia Research Institute of Agricultural Biotechnology and the Shemyakin–Ovchinnikov Institute of Bioorganic Chemistry, RAS) [9] and a shortened earing and maturation time of common wheat varieties (Kurchatov Genomic Center, Institute of Cytology and Genetics, SB RAS—<http://www.ras.ru/news/shownews.aspx?id=e327e268-7875-4046-bb4f-dbd940d270d&print=1>) [10].

- Increased resistance of potatoes to saccharification under cold exposure and long-term low-temperature storage, achieved by genome editing (Kurchatov

Genomic Center, and the RAS Federal Research Center “Fundamentals of Biotechnology”) [11].

Equally topical is the use of genetic technologies in industrial biotechnology, which has a difficult history in our country. Although powerful in the 1970s, the domestic industry—the microbiological industry, which produced essential amino acids, vitamins, enzymes, and antibiotics—was practically destroyed in the 1990s. The country was faced with the need to import these products from abroad. Now there are good prospects for growth in this industry. For example, the Federal Scientific and Technical Program for the Development of Genetic Technologies for 2019–2027 plans to develop at least 25 strains and/or microbial consortia—producers of biologically active substances (essential amino acids, enzymes, and vitamins). Several complexes have already been launched for deep processing of grain and the production of amino acids, primarily lysine—a feed additive that ensures high efficiency in animal husbandry. These are Premix Factory no. 1 with a capacity of 80 000 t per year in Belgorod oblast (<https://www.lysine31.ru>) and AminoSib with a capacity of 30 000 t per year in Tyumen’ oblast (<https://aminosib.ru/lizin/>). Two factories to produce enzymes for the food industry and agriculture—Agroferment (Tambov) and Sibbiopharm (Novosibirsk oblast)—function stably. Undoubtedly, the production of modern products requires new producer strains and innovative methods of genetic engineering, including genome editing.

Updating the regulatory framework for the use of products of genetic technologies. The widespread use of GTs is hindered by the legal system in force in Russia. It is still forbidden to use genetic engineering in agricultural production to improve plant varieties and animal breeds (Federal Law no. 7-FZ On Environmental Protection, p. 50). The domestic agricultural producer is excluded from the most effective and high-tech methods for solving food problems that are already widely used abroad. Argentina’s approval of HB4® drought-tolerant GM wheat for commercial use in 2020 is a prime example of this demand. In dry years, it provides a yield increase of 20%. The entry of this GM wheat into the market could lead to a fundamental redistribution in the world grain trade.

The ban declared by Federal Law no. 7-FZ threatens Russia not only with a loss in the global agricultural market but also with a loss of control over the circulation of genetically engineered products on its territory. The point is that due to the improvement of gene modification methods, the final product of genome editing are organisms with acquired valuable properties and with no foreign DNA in their genome. In this case, it is fundamentally impossible to establish the fact of the use of genome editing and to control and regulate the release of its products. Therefore, it is important to clarify the fundamental principles of regulation (with account for the modernization of tech-

nologies) and determine the legal status of the final products of GTs for the formation of a legal environment in various areas of their application. In this context, it is necessary to shift the focus of legal control from genetic technologies to their final product.

Today, many countries use the concept of product-oriented regulation in the field of GTs. This approach is based on the characteristics of the new product, regardless of how it has been obtained. This concept is followed by leader countries of biotechnological production: Canada, the United States, the BRICS countries, and Latin America led by Argentina, a pioneer in the legal regulation of GT products, as well as Japan and Korea. With a focus on product-oriented regulation, UK legislation is being revised.

In Russia, the imperfection of legal regulation in the field of genetic engineering activities (GEA) is largely due to the “legal decay” of basic Federal Law no. 86-FZ On State Regulation in the Field of Genetic Engineering Activities [12]. In the 1990s, its provisions formed the basis of the country’s stringent biosecurity system for classical transgenic organisms (GMOs). However, over the last 25 years, completely new, breakthrough technologies have appeared, unknown in 1996, which requires a revision of approaches to regulating the use of their products.

An important challenge today is that Law no. 86-FZ lacks a modern nomenclature relevant for new genetic technologies. The fundamental conceptual gap in it is the lack of a scientific definition for *genetically edited* organisms that are obtained thanks to innovative GTs and are not transgenes in terms of their biological nature. In this regard, the scientific community is discussing the question, “Is gene editing genetic engineering or not?”; and after it, “Is it worth it to work on the genome editing of agricultural plants and animals?” “Pure science,” which is not forbidden as such, is of little interest to anyone now: the real economy needs practical innovation and an economic effect. Technologically, genome editing is undoubtedly genetic engineering since it uses genetic engineering methods (note that Law no. 86-FZ relies on methods). Since the law does not provide for organisms other than transgenic ones, all edited organisms automatically become transgenic. From a biological point of view, this is not always the case. A classical transgenic organism always contains inserts of foreign, recombinant DNA in its genome and therefore can be identified by laboratory methods. An organism obtained by genome editing methods either contains foreign DNA, and then it is transgenic, or it has only targeted point changes in the genome (individual nucleotides are replaced). It is obvious that such changes are in no way different from natural mutations. However, even small mutations can make a huge difference to humans.

An interesting example is when just one mutation in one nucleotide turned the whole history of agronomy

upside down. It was a mutation in the *Q* gene, located on chromosome 5A of the wild wheat genome, which resulted in a single amino acid change in the encoded protein. As a result, the wheat ear ceased to be brittle, and the grain was no longer filmy. Such wheat changed the whole mode of agriculture, the food industry, and civilization as a whole.

Most valuable forms of agricultural crops arose in a similar way, as a result of mutations that knocked out a gene that was beneficial for the body in natural conditions and at the same time undesirable for humans in agricultural cultivation. Previously, it took people centuries to find such natural mutations and introduce them into agricultural crops. At present, such mutations can be intentionally and fairly quickly obtained by genome editing, but then no one, except the producer, can say whether genetic engineering has been used in this case or whether this is classical mutagenesis.

In the context of technology modernization, it becomes obvious that it is time to revise Law no. 86-FZ, the basic law on genetic engineering. Such a revision primarily concerns fundamentally important changes in the nomenclature. The new edition of the law should include the following main goals:

- to separate the notions of *transgenic organism* and *genetically edited organism*;
- to replace the object of the law’s regulation—a technological process (genetic engineering activity)—with a scientifically and economically justified new object—the product of genetic modification (GM product), regardless of the method of production, with an assessment of the safety of the product.

The very definition of genetic engineering, given in 1996, also needs revision: *genetic engineering* is a set of methods and technologies, including technologies for obtaining recombinant ribonucleic and deoxyribonucleic acids, for isolating genes from an organism, manipulating genes, and introducing them into other organisms. The reason is that “manipulating genes and introducing them into other organisms” can be performed not only by genetic engineering methods but also by classical genetics methods. The new wording shifts the emphasis of the definition to the *goal of activity* (genetic engineering)—obtaining organisms with various types of genome modification. In this case, “*genetic engineering/gene engineering* is a set of methods and technologies for obtaining recombinant ribonucleic and deoxyribonucleic acids, including those used to obtain genetically modified organisms and genetically engineered organisms.”

Additionally, for the first time, it is proposed to introduce the notion of *recombinant DNA/RNA*, which was not previously enshrined in Federal Law no. 86-FZ but is a key notion for modern genetic engineering, based entirely on manipulations with recombinant molecules. It has steadily been developed as a biological term but has not been defined as a criterion

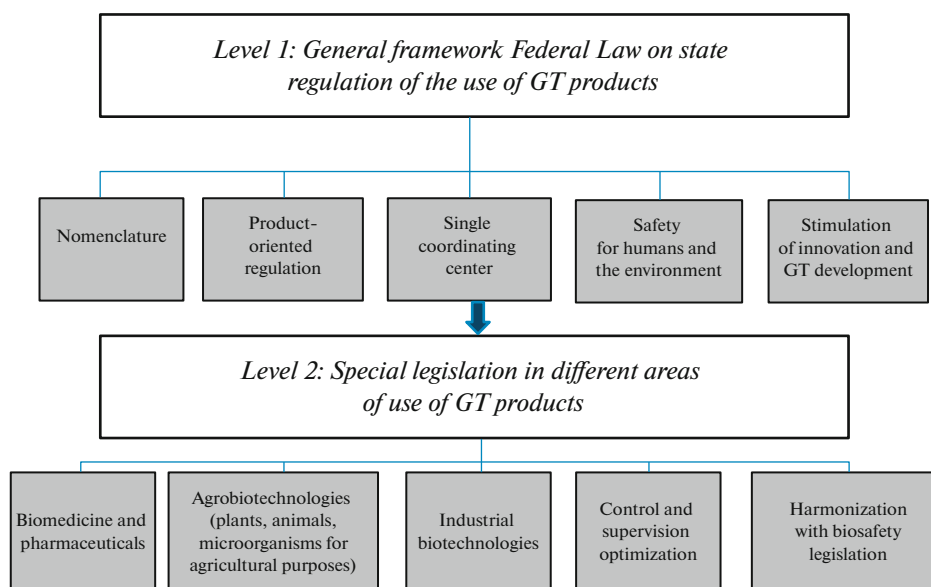


Fig. 1. Structured legal framework for the regulation of genetic technology products.

for the purposes of legal regulation. “*Recombinant ribonucleic or deoxyribonucleic acid* is DNA or RNA molecules obtained by laboratory methods (molecular cloning, synthesis) and having nucleotide sequences that are not found in the genomes of objects of genetic engineering activities and the genomes of closely related natural species.”

As was emphasized above, the transition to product-oriented legal regulation is dictated by life itself (the development of technology and the demands of the economy). To solve this problem, it is proposed to introduce a new notion into Law no. 86-FZ, *product of genetic engineering activity*. “*The product of genetic engineering activity* is recombinant nucleic and deoxyribonucleic acids, genetically modified and genetically edited organisms, as well as products obtained using such organisms.”

The key innovation in the updated nomenclature is the introduction of a notion necessary to define organisms obtained by new technologies, in particular, genome editing methods. In their final status, they are not genetically modified organisms. “*A genetically engineered edited organism (GEEO)* is an organism whose genotype has been purposefully modified using genetic engineering methods and whose genetic material does not contain recombinant DNA or RNA inserts.”

The notion of a *transgenic organism* is fundamentally preserved, but in an updated definition. “*A genetically modified organism (GMO), or transgenic organism*, is an organism the genotype of which has been purposefully changed using genetic engineering methods, as a result of which the genetic material of the organism contains recombinant ribonucleic and/or deoxyribonucleic acid inserts.” The new definition of

a transgenic organism is expressed through the notion of *recombinant DNA/RNA*, which connects it with the notion of *genetic engineering* in both the old and the new edition.

Federal Law no. 86-FZ contains other legal inconsistencies with modern scientific knowledge and realities. The current norm of the law (clause 8, article 7) blocks the development and operation of Russian industrial biotech enterprises, while all over the world industrial microbiology is a basic growing area with a significant contribution to the implementation of the climate strategy and the low-carbon economy.

To fulfill *the task* set by the country’s leadership *for the development and use of GTs*, it is necessary to form a comprehensive and scientifically substantiated legal regulation in this area, which at the same time should ensure their biosafety for human health and the environment and legal clarity of GT products and their use.

The concept of legal regulation of the use of genetic technology products in Russia. Based on the results of the analysis of legislative norms in GEA, a concept of legal regulation of the use of products of genetic technologies in Russia has been developed (Fig. 1). It provides for two stages of implementation: first, the creation of a consolidating framework federal law, including an updated nomenclature and issues of security, innovation stimulation, and GT development; second, the development of a special regulatory framework for the use of GEA products with account for the characteristics of a particular sector of the economy and the social sphere.

Figure 1 shows only a few main directions:

- biomedicine and pharmaceuticals;

- agrobiotechnologies with their objects: plants, animals, and agricultural microorganisms. There is a need for scientifically based solutions aimed at the optimal practical use of GT products in the real sector of the economy. The specifics of Russian agrobiotechnological developments should be taken into account in the normative acts under formation;

- industrial and ecological biotechnologies are a growing trend;

- optimization of control and supervision. New technologies in GEA will certainly require significant adjustment and development of the legal system that would ensure the safety of the use of multidirectional products of genetic technologies.

An important component of the proposed concept is the harmonization of the legal regulation of the production and circulation of genetic technology products, primarily within our country, with account for the interests of domestic producers. To solve this problem, it is advisable to establish a single interdepartmental center responsible for implementing the concept of the development of genetic technologies and legal regulation of the use of their products. Its activities should ensure the unity of the fundamental principles of regulation that is missing today in various areas of using the achievements of modern GTs. Such powers may be delegated to one of the current executive authorities.

* * *

Let us formulate proposals on priority measures for updating the Russian regulatory framework for the creation and use of GT products:

- bringing the norms of outdated Law no. 86-FZ in line with the current level of development of science in the field of genetic technologies, including the adjustment of the nomenclature of genetic engineering activities, as a key approach to updating the regulation of the use of genetic technology products;

- distinction between the terms of *transgenic organism* and *an organism with targeted changes in the genome without introducing foreign DNA into it*;

- reforming the concept of Russian legislation by shifting its focus to the control of the safety of the GT product;

- improvement of control and supervision over the use of products of genetic technologies;

- adjustment of Russian legislation in terms of regulations aimed at regulating the industrial use of GM microorganisms in closed systems.

These proposals were considered and supported by most respondents during a survey of members of the Vavilov Society of Geneticists and Breeders, which unites about 3000 specialists in the field of genetics and breeding.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Decree of the President of the Russian Federation of November 28, 2018, No. 680, On the Development of Genetic Technologies in the Russian Federation. <http://publication.pravo.gov.ru/Document/View/0001201811280061?rangeSize=1>.
2. Decree of the President of the Russian Federation of July 21, 2016, No. 350, On Measures to Implement the State Scientific and Technical Policy in the Interests of the Development of Agriculture, *Sobr. Zakonodat. RF*, No. 30, Article 4904 (2016). <http://pravo.gov.ru/proxy/ips/?docbody=&firstDoc=1&lastDoc=1&nd=102404049>.
3. I. G. Atabekov, *Realization of Genetic Information* (Nauka, Moscow, 1972) [in Russian].
4. A. S. Zadorin, M. V. Sukhacheva, B. B. Kuznetsov, et al., "Identification of a unique transformation event in potato of *Elizaveta plus* line resistant to Colorado beetle," *Biotechnol. Russ.*, No. 3, 45–52 (2008).
5. A. M. Kamionskaya, B. B. Kuznetsov, V. Y. Ismailov, et al., "Genetically transforming Russian potato cultivars for resistance to Colorado beetle," *Clon. Transgen.* **1** (1), 101 (2012).
6. S. A. Tyurin, Yu. I. Mashkov, I. N. Yakovleva, et al., "The Basic approaches to design of strains producing preparations for plant protection. II. A strain of the bacterium *Bacillus thuringiensis ssp. kurstaki* with insecticidal activity against representatives of the orders *Lepidoptera*, *Coleoptera*, and *Homoptera*," *Biotechnol. Russ.*, No. 3, 38–49 (2006).
7. L. K. Ernst, N. A. Zinov'eva, and G. Brem, *Transgenic Animals and Possibilities of Their Use: Molecular Genetic Aspects of Transgenesis in Animal Husbandry* (VIZh, Moscow, 2001) [in Russian].
8. T. V. Matveeva and L. Otten, "Widespread occurrence of natural genetic transformation of plants by *Agrobacterium*," *Plant. Mol. Biol.* **101**, 415–437 (2019).
9. M. S. Bazhenov, A. G. Chernook, L. A. Bespalova, et al., "Alleles of the GRF3-2A gene in wheat and their agronomic value," *Int. J. Mol. Sci.* **22** (22), 12376 (2021).
10. A. Berezhnaya, A. Kiseleva, I. Leonova, and E. Salina, "Allelic variation analysis at the vernalization response and photoperiod genes in Russian wheat varieties identified two novel alleles of Vrn-B3," *Biomolecules* **11** (12), 1897 (2021).
11. M. A. Slugina, M. A. Filyushin, A. A. Meleshin, et al., "Differences in the amylase inhibitor gene SbAI expression in potato during long cold storage and in response to short-term cold stress," *Russ. J. Genet.* **56** (3) 375–378 (2020).
12. I. V. Korobko, P. G. Georgiev, K. G. Skryabin, and M. P. Kirpichnikov, "GMOs in Russia: Research, society, and legislation," *Acta Naturae* (English-language version) **8** (4), 6–13 (2016).

Translated by B. Alekseev