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POTENTIAL RISKS OF OCCUPATIONAL EXPOSURE TO INNOVATIVE BIOPHARMACEUTICALS: A REVIEW

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Introduction. Gene-targeted therapies (gene-targeted, high-tech, and biopharmaceuticals) are developed based on active pharmaceutical ingredients, which are reactive compounds with pleiotropic activity. Such ingredients are associated with health hazards to workers employed at various stages of their production. Clinically significant pharmacological or toxicological effects of innovative medications on employees exposed to these components are unsafe from the perspective of a risk-based approach in occupational medicine.

Objective. Assessment of potential risks of occupational exposure to innovative biopharmaceuticals in production or laboratory conditions and approaches to their hygienic management.

Materials and methods. The relevant scientific publications were searched and retrieved via electronic bibliographic databases both in the Russian language (eLibrary, CyberLeninka) and in the English language (WoS, Scopus, PubMed). Regulatory documents were analyzed using the *Consultant Plus* legal information system.

Discussion. Specific features of production of new-generation biopharmaceuticals (gene-targeted, high-tech, or biotechnological medications) and the associated risks of occupational exposure to workers in pharmaceutical or laboratory production are considered. It was established that employees of such enterprises are exposed to the combined influence of adverse — biological, physical, and chemical — production environment factors. There is a lack of information on the development of analytical methods for identifying gene-targeted components (high-tech or biotechnological medications) in the workplace air and wastewater, as well as on workplace surfaces. The identified problems of occupational health are related to the lack of legislative instruments and knowledge-based management decisions on the identification of risk factors and control ranges of potential work-related effects of innovative biopharmaceuticals. Such approaches should be based on the principles of hygienic regulation aimed at eliminating or reducing negative industrial effects and ensuring the safety and preservation of employee health.

Conclusions. Major methodological approaches to assessing the work-related impact of gene-targeted, high-tech, or biotechnological therapies on employees of pharmaceutical enterprises are determined. These approaches include: (1) toxicological assessment of compounds with the establishment of possible parameters of toxicometry; (2) evaluation of the pharmacological and toxicokinetic features of gene-targeted therapeutical components; (3) development of methods for their quantitative determination in various environments; (4) establishment of biomarkers of exposure and related effects followed by hygienic rationing and justification of preventive measures.

Keywords: advanced therapy medicinal products; gene therapy medicinal product; biotechnology-derived pharmaceuticals; preclinical studies; monoclonal antibodies; occupational hazard; allowable concentrations

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ВОЗМОЖНЫЕ РИСКИ ПРОФЕССИОНАЛЬНОГО ВОЗДЕЙСТВИЯ ИННОВАЦИОННЫХ БИОЛОГИЧЕСКИХ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ: ОБЗОР ЛИТЕРАТУРЫ

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Введение. Активные фармацевтические ингредиенты для производства лекарственных препаратов, воздействующих на генетический аппарат (генотерапевтических, высокотехнологических, биотехнологических), являются реакционноспособными соединениями с плейотропной активностью, что сопряжено с рисками здоровью работников, занятых на различных этапах их производства. Клинически значимый фармако/токсикологический эффект инновационных лекарственных препаратов, воздействующих на работающих, имеющих производственный контакт с данными компонентами, с точки зрения риск-ориентированного подхода в медицине труда является небезопасным.

Цель. Оценка потенциальных рисков профессионального воздействия инновационных биологических лекарственных препаратов на работающих в условиях производства/лаборатории и методических подходов их гигиенической регламентации.

Материалы и методы. Поиск научной литературы выполнен в электронных библиографических базах данных на русском (eLibrary, CyberLeninka) и английском (Web of Science, Scopus, PubMed) языках, нормативных документах в справочной правовой системе КонсультантПлюс.

Обсуждение. Рассмотрены отдельные аспекты особенностей разработки биологических лекарственных препаратов нового поколения (генотерапевтических/высокотехнологических/биотехнологических лекарственных средств) и сопряженных с этим рисков профессионального воздействия на работников в условиях фармацевтического или лабораторного производства. Выявлено, что работники подвергаются сочетанному воздействию неблагоприятных факторов производственной среды различной природы: биологических, физических, химических. Отмечается неполнота информации о разработке аналитических методов идентификации компонентов генотерапевтических/высокотехнологических/биотехнологических лекарственных средств в воздухе рабочей зоны, на рабочих поверхностях, в сточных водах. Обозначены актуальные проблемы гигиены труда, связанные с отсутствием законодательных инструментов, научно обоснованных управленческих решений по идентификации факторов риска здоровью работников, диапазонов контроля потенциального производственного воздействия инновационных биологических

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лекарственных препаратов на основе принципов гигиенической регламентации, направленной на устранение или уменьшение негативного производственного воздействия и обеспечение безопасности и сохранения здоровья работников.

Выводы. Проведенная работа позволила определить основные методические подходы по оценке потенциального производственного воздействия генотерапевтических/высокотехнологических/биотехнологических лекарственных средств на работников соответствующих фармацевтических предприятий. К таким подходам относятся: токсикологическая оценка соединений с установлением возможных параметров токсикометрии, исследование фармако/токсикокинетических особенностей компонентов генных препаратов, разработка методик их количественного определения в различных средах, установление биомаркеров экспозиции и эффекта с последующим гигиеническим нормированием и обоснованием основных профилактических мероприятий.

Ключевые слова: высокотехнологичный лекарственный препарат; генотерапевтический лекарственный препарат; биотехнологический лекарственный препарат; доклинические исследования; моноклональные антитела; профессиональный риск; предельно допустимая концентрация

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INTRODUCTION

Modern medicine has reached a high level of development in the fields of innovative technologies and innovative medicinal products (MPs). Unfortunately, for a number of diseases, not only etiotropic but also pathogenetic therapeutical approaches are still lacking [1].

Until recently, the pharmaceutical industry has been largely aimed at the creation and industrial production of low-molecular weight MPs. However, the evolving understanding of the possibility of affecting the genetic apparatus of somatic cells to restore or modify the synthesis of certain proteins associated with a particular disease has led to the appearance of innovative biological MPs [2–4] for treating a wide range of conditions.

Active pharmaceutical ingredients currently used for the production of gene-targeted MPs are reactive compounds with pleiotropic activity. Such ingredients can carry health risks for workers involved in various stages of their production [5]. Although the effects of MPs on patients may be desirable or acceptable, any clinically significant pharmacological or toxicological effect of a gene-targeted MP on people working with these components is unsafe from the perspective of a risk-based approach in occupational medicine [6–7]. The priority direction of preventive medicine consists in identification of unsafe production factors and evaluation of safe exposure limits to hazardous factors at the workplace for the purpose of their hygienic control, based on the principles of safety for workers, the environment, and the public.

In this work, we aim to assess potential risks of occupational exposure of workers to innovative biological medicinal products in production or laboratory conditions and to determine approaches for their hygienic management.

MATERIALS AND METHODS

Scientific publications on the topic under study were searched and retrieved via electronic bibliographic databases in the Russian (eLibrary, CyberLeninka) and English (WoS, Scopus, PubMed) languages. Regulatory documents were analyzed using the *Consultant Plus* legal information system. Search queries were carried out using the following keywords: advanced therapy medicinal product (ATMP), gene therapy medicinal product (GTMP), biotechnology-derived pharmaceuticals, preclinical studies, monoclonal antibodies (mAbs), occupational hazard, and allowable concentration. The search depth was 10 years. The inclusion criteria were: availability of structured information on preclinical and clinical safety of ATMPs, GTMPs, biotechnology-derived pharmaceuticals, quantitative methods of their identification in different environments, as well as specific features of production environment control.

RESULTS AND DISCUSSION

Modern therapeutic strategies are aimed at individualization of therapeutic effects, adapting the medication and dose to the needs of a particular patient. Such strategies can be realized through the use of biological or biotechnological products capable of modifying gene sequences or controlling their expression, as well as those changing the biological properties of cells and, accordingly, the production of therapeutically active proteins in the body for their therapeutic or preventive effects [8–9].

According to the report “Gene Therapy Development & Manufacturing 2023”, more than 3150 biological, biotechnological, and gene-targeted new-generation MPs are currently undergoing various R&D stages, with more than two dozen drugs having been approved for clinical use by MP regulatory authorities of different countries [10].

In the Russian Federation, the R&D, expertise, production, and introduction of biological or biotechnological MPs into healthcare practice is an actively growing direction. At the same time, gene therapy is still defined as a set of genetic engineering (biotechnological) and medical methods aimed at introducing changes in the genetic

apparatus of human somatic cells in order to treat diseases [11]. Recently, the regulative documentation in this sphere has undergone revision, evidenced by the adoption of the Federal Scientific and Technical Program for the Development of Genetic Technologies for 2019–2027. This program is aimed at solving the problems of accelerated development of genetic technologies, including genetic editing technologies [12–14].

At the same time, according to the Federal Law No. 61-FZ "On Circulation of Medicinal products" dated 12.04.2010 (ed. 30.01.2024) clause 6.3, art. 4, the following definition is introduced: "advanced therapy medicinal product is a gene therapy medicinal product (GTMP) for medical use or an MP based on somatic cells for medical use or a tissue-engineered MP (tissue engineering product)." Clause 7.2 of art. 4 of this law and the EAEU Decision No. 78 of 03.11.2016 "On the Rules for Registration and Examination of Medicinal Products for Medical Use" defines GTMP as follows: "a biological MP containing an active substance with recombinant nucleic acid or consisting thereof, administered to a person for the purpose of regulating, restoring, replacing, adding, or deleting a genetic sequence. Clause 7.1 of art. 4 of the same law specifies the definition of biotechnological MPs, namely, the production of which is carried out using biotechnological processes and methods. The latter feature DNA recombinant technology, technology for controlled expression of genes encoding biologically active proteins in prokaryotes and eukaryotes, including modified mammalian cells), hybridoma and monoclonal antibody methods.

Along with the abovementioned, according to the RF Federal Law No. 180-FZ of 23.06.2016, the term "biomedical cell product — a complex consisting of a cell line (cell lines) and auxiliary substances, which do not include transplantation objects, as well as advanced therapy medicinal product, including GTMPs" applies to biomedical cell products. Requirements for production conditions, validation of the production process, quality control of target and intermediate products of GTMPs are reflected in the National Standard of the Russian Federation GOST R 52249-2009 "Rules of production and quality control of medicinal products" and the State Pharmacopoeia of the Russian Federation XIV OFS.1.7.1.0011.18 "Biotechnological medicinal products." Methodology and requirements for conducting preclinical studies, stability studies of biotechnological pharmaceuticals, and safety of pharmaceutical substance and finished dosage form are described in the national standard GOST R 57688-2017 "Medicinal products for medical use. Stability studies of biotechnological/biological medicinal products."

It should be noted that the aforementioned legal framework regulates the processes of biological or biotechnological MP circulation, being primarily aimed at ensuring the quality and safety of biological or biotechnological MPs. However, it does not guarantee the health safety of personnel having occupational contact with harmful or hazardous factors at the workplace.

In the Russian Federation, the legislative basis for occupational medicine, i.e., a branch aimed at protecting the health of the working contingent in contact with harmful or hazardous factors of the working environment (physical, chemical, biological, and occupational factors), is formed by a wide range of existing normative and methodological or legal documents, which were significantly amended in the period from 2021 to 2022. These amendments reflect modern requirements for occupational safety and health protection of the working population in accordance with international standards and new achievements in science and technology.

Thus, according to the Sanitary Rules and Regulations 3.3686-21 "Sanitary and Epidemiological Requirements for the Prevention of Infectious Diseases", mandatory requirements for a set of organizational, sanitary, and anti-epidemic, therapeutic and preventive, laboratory-diagnostic, engineering and technological measures are established, along with the order of accounting, storage, transfer and transportation, conditions and algorithm of work at the molecular, cellular levels for the creation of modified or genetically engineered variants of biological agents, diagnostic tests, and diagnostic procedures.

An important point in the recently adopted Decree of the President of the Russian Federation of March 11, 2019 No. 97 "On the Fundamentals of the State Policy of the Russian Federation in the Field of Ensuring Chemical and Biological Safety for the Period up to 2025 and Beyond" was the definition of strategic directions of the state policy in the field of ensuring biological safety. These include maintaining an acceptable level of risk of negative impact of hazardous biological factors on the population and the environment; development of hygienic standards and methods for indicating the content of biological agents in the environment; implementation of modern mechanisms for managing chemical and biological risks; implementation of a set of measures to prevent and minimize biological risks, increase the protection of the population and the environment from the negative impact of hazardous biological factors, as well as assessment of the effectiveness of these measures.

The issues concerning the methodology of development and scientific substantiation of criteria for hygienic assessment of the impact of biological production factors are of particular significance. It should be noted that at the legislative level, there are currently no clear indications of the procedure of industrial control and algorithms for hygienic rationing of harmful factors of the working environment arising at various stages of development and production of GTMP, ATMP, biotechnological MPs, both in the workplace air and in environmental objects.

Industrial biotechnologies, according to GOST R 52249-2009 National Standard "Rules of production and quality control of medicines", represent multistage technological processes, based on the use of different strains and serotypes of living microorganisms, cell cultivation or extraction of material from living organisms, a wide range of raw materials, the formation of a wide range of intermediate and end products of microbial synthesis. This determines the complex nature of harmful effects associated with the process of biological and microbial synthesis and, therefore, the combined nature of harmful effects of biological and other production factors on the body of workers [10, 11].

The general biotechnological scheme of pharmaceutical production includes five stages: strain selection, selection and preparation of nutrient medium, cultivation of strain-producers (fermentation), obtaining inoculum, isolation and purification of the target product. Biotechnological pharmaceuticals require a high degree of purity, which is achieved by successive purification operations, such as separation, destruction of cell membranes (biomass disintegration), separation of cell walls, separation and purification of the product, fine purification and separation of preparations. It should be noted that separation and purification of the product with subsequent separation of preparations and isolation of the target product from the culture fluid or homogenate of destroyed cells is carried out by precipitation (salting), extraction, or adsorption. During this precipitation process, physical (heating, cooling, dilution, concentration) and chemical methods (using inorganic and organic substances — ethanol, methanol, acetone, isopropanol) are applied [11, 12, 13, 14], which creates an additional load in terms of air pollution at the workplace by chemical organic and inorganic compounds.

During production, pharmaceutical ingredients may be released into the workplace air, as a rule, in trace amounts or in high concentrations in emergency situations. Such events may occur in case of non-compliance with sanitary and hygienic requirements, e.g., insufficient sealing of equipment at various stages of the technological process. This may result in contamination of the workplace air, clothing, skin of workers, surfaces of equipment, building structures, industrial sites, and the broader environment. In the air of industrial premises, harmful substances can be found in the form of gases, vapors, aerosols, as well as in the form of mixtures. These substances enter the body mainly through the respiratory tract (inhalation), gastrointestinal tract (orally), skin (transcutaneously), and through the mucous membrane of the eyes in some cases [10, 12, 13, 14].

The risk of inhalation exposure to components of biologic or biotech MPs (detailed in WHO/CDS/CSR/ISR/99.2. Department of Communicable Disease Surveillance and Response) is possible through the following manufacturing manipulations: bacteriological loop calcination, seeding on agar dishes, pipetting, swab preparation, opening cell culture vessels, blood or serum sample collection, centrifugation; the risk of ingestion of a pathogenic agent is likely when handling samples, swabs and cultures; the risk of subcutaneous infection is likely when using needles and syringes when handling blood or removing infected material.

In recent years, the number of therapeutic agents developed on the basis of genetically engineered monoclonal antibodies (mAbs), such as bevacizumab, cetuximab, daratumumab, omalizumab, rituximab, and trastuzumab, has increased significantly. Such agents occupy one of the leading positions in the global pharmaceutical market in terms of production volume [15–17]. As of November 2021, more than 130 antibody-based drugs have been approved or are under consideration by regulatory authorities. In the world's clinical practice, about 35 mAb medications are used for the treatment of oncological, autoimmune, infectious, and allergic diseases characterized by a long progressive course. In Russia, about 23 mAb medications have been registered and are successfully used [14, 18].

As a rule, monoclonal antibodies are large molecules with a molecular mass > 140 kDa, designed for targeting specific proteins [15, 19, 20]. Bispecific monoclonal antibodies (bsAbs) are next-generation antibodies, typically having molecular masses between 50 and 60 kDa, with higher clinical efficacy and safety by targeting two different immunoregulatory pathways. Monoclonal antibodies are produced using hybridoma technology, recombinant DNA, or other technologies [21–23].

The active component of mAb medicines are highly purified immunoglobulins or their fragments, e.g., F(ab') 2-fragments, characterized by specificity to a strictly defined antigen determinant, produced by one clone of antibody-forming cells. The source of mAb production is cloned cells — immortalized ("immortal") B-lymphocytes in the form of a transplanted cell culture or cell line, obtained on the basis of recombinant DNA technology [18, 22]. Immunoglobulins or their fragments can be altered by various modifications: conjugation with a toxin, inclusion of a radioactive tag, chemical binding of two immunoglobulin molecules or their derivatives to obtain an mAbs with dual specificity, creation of Fc-linked fusion proteins — fusion proteins, etc. [16, 19].

Monoclonal antibodies exhibit unusual characteristics. These are large-molecule proteins that are hydrophilic and labile (both chemically and enzymatically), which allows them to be broken down in the gastrointestinal tract. However, these are stable molecules with a long half-life, usually several days or weeks [20, 21]. In addition, according to Brian A. Baldo, conjugation with polyethylene glycol (PEG) or pegylation of mAb further prolongs their half-life and creates additional safety problems associated with the lack of biodegradability of the PEG component [22].

Taft et al. found that for monoclonal antibodies, due to their inherent high specificity of binding and affinity to their target, the main pathway of elimination is target-mediated distribution of drugs, especially at low doses and concentrations [23]. This is the phenomenon of targeted "binding" of a compound, in particular, a monoclonal antibody to a target cell with a receptor type strictly specific thereto. In this case, a small amount of the drug substance is required for the onset of the therapeutic effect [24], which is a favorable criterion for the clinical use of mAb, although significantly increasing the potential risk of occupational exposure of workers to the conditions of its industrial production.

Brian A. Baldo et al. note that adverse reactions from the immune system obtained during clinical observations of mAb use are hypersensitivity reactions, such as anaphylaxis, skin manifestations, generalized cytokine reactions, decreased immune system function, and autoimmune reactions [25].

According to Lars et al., during various technological stages of development and production, protein preparations, including mAb, can be found in the workplace air in the form of gases, vapors, aerosols, and gas-vapor-aerosol mixtures. Such preparations may cause undesirable

side effects in workers of biopharmaceutical companies [26]. Given the vast surface area (more than 100 m^2) of the lining of the pulmonary epithelium, which is in close contact with a wide network of capillaries, the absorption of foreign substances through the lungs by the inhalation route can occur at a high rate [10, 22, 27]. At the same time, the rate of particle settling in the respiratory tract epithelium directly depends on the size of the respirable fraction. Thus, particles larger than 10 μm settle in the nasopharynx and tracheobronchial section (in these sections of the respiratory tract, the epithelium is thicker and covered with a layer of mucus). This limits systemic absorption, not excluding the development of local reactions. In addition, the ciliated epithelium moves mucus-containing particles to the pharynx, where it is swallowed and enters the gastrointestinal tract [28].

Some studies have established that the transport of molecules larger than 0.6 nm through cell layers into the blood via inhalation of protein drugs (mAb, bispecific antibodies, fusion proteins) is provided by alveolar epithelial cells having pores and vesicles by passive diffusion with further manifestation of their systemic effect on the organism [29]. At the same time, recent studies have described that, for larger proteins (>40 kDa), the dominant mechanism of transmembrane protein transport is receptor-mediated transcytosis via the neonatal Fc receptor (FcRn). This mechanism is expressed in the primate upper airways, rat bronchial and alveolar cells with an inherent ability to bind to high affinity proteins, which plays an important role in the transport of IgG to other tissues [30–32]. At the same time, both transcytosis and paracellular mechanisms may be important for smaller proteins [33–35].

Experimental studies by Dumont et al. found that during inhalation exposure of monkeys to protein preparations (including mAb), the level of absorption of IgG1 Fc-domain complex deposited in the lungs was equal to the blood level of protein preparation/mAb during subcutaneous injection in primates and humans [36]. This creates preconditions for accumulation of these preparations in the lung tissue, which can have a negative impact on the organism of workers in the conditions of production at all stages of the technological process.

In a study by Fahy et al. conducted on healthy volunteers, production inhalation exposure to mAb: E25 or omalizumab with a daily exposure via nebulizer 10 min for 56 days was modeled. It was found that more than 15% of the administered medication dose was actually deposited in the alveoli, and the systemic bioavailability of E25 or omalizumab by inhalation ranged within 1.6–4.3% [37–39]. This finding is important for specialists in occupational medicine, since the mAb aggregated in the lungs, even after partial intracellular enzymatic destruction by pulmonary antiproteases, may initiate a cascade of pathological processes in the lung tissue [40]. This should be taken into account when developing regulations for occupational exposure both in the workplace air and in the biological environments of the corresponding pharmaceutical production facilities.

In [41–42], recommendations for establishing occupational exposure limits for monoclonal antibodies and fusion proteins in the workplace air at the level of ≥1 μg/m^3 by inhalation route of entry, taking into account the systemic bioavailability after inhalation of less than 1% for compounds with molecular mass >10 kDa, were proposed.

GTMPs can be used to deliver therapeutic genes into target cells; however, neither DNA nor RNA in free form can be used to achieve this goal due to a rather rapid degradation of nucleic acid in serum under the influence of nucleases. Therefore, vector genetic constructs have been developed for gene delivery into eukaryotic cells since the early 1980s [43]. To date, five major classes of viral vectors have been tested as gene delivery vectors for clinical use, including retroviruses, adenoviruses, adeno-associated viruses, lentiviruses, and herpes simplex viruses [44–45].

According to the data of several clinical and preclinical studies, a number of side effects have been found in GTMPs/ATMPs based on viral vector systems. Thus, some researchers noted that genetic changes mediated by drugs using retroviral vectors with replication deficiency caused manifestations of insertional mutagenesis and malignant transformation of hematopoietic progenitor cells with the development of acute myeloid leukemia and lymphoproliferative diseases [46].

The studies by Ott et al. provided evidence for retroviral vector-induced negative effects on hematopoietic activity, manifested in restoration of oxidative antimicrobial activity in phagocytes after gene transfer, significant gene transfer into neutrophil cells with the formation of a large number of functional phagocytes, and expansion of gene-corrected myelopoiesis with progression toward myelodysplasia [47–48].

Unlike GTMP using retroviral vectors, adenoviral vector-based preparations do not replicate and are not oncogenic. However, they exhibit a pronounced immunogenicity [49] with the activation of immunocompetent cells. These, in turn, begin to secrete cytokines and chemotaxis factors that attract neutrophils, macrophages, and natural killer cells to the focus and trigger an immune response with the production of specific antibodies after several days. Various target cells *in vitro* and several mouse models *in vivo* found that some first-generation adenoviral vectors, which retain a significant part of the genome, are capable of initiating dose-dependent apoptosis, i.e., exhibit direct cytotoxicity [50–51]. Several episodes of inflammatory reaction to adenoviral vectors, including the development of severe hepatotoxicity with lethal outcome, have also been reported in clinical trials [52].

Adeno-associated vectors are among the most common vectors used in gene-targeted therapy, although their use can result in undesirable inadvertent activation or inhibition of endogenous gene expression and infection in primates and humans [53–54].

Lentiviral vectors are derived from HIV-1 and are capable of affecting both dividing and non-dividing cells, making them a potential vector for gene transfer *in vivo*. Most lentiviral vectors retain the ability to integrate into the genome of infected cells; deletion of many HIV proteins reduces the probability of formation of a virus capable of replication in the human body [55]. To obtain pseudotyped lentiviral vectors, envelope glycoproteins of viruses considered to be

potential agents of biological weapons (Ebola, Marburg, Ross River hemorrhagic fever viruses, etc.) are used. Therefore, their use in research is still associated with potential risks, and the long-term safety of these clinical interventions is still being evaluated [56].

Herpesvirus-based vectors provide long-term transgene expression, are neurotrophic and highly effective in studying retrograde and anterograde transport in CNS. However, they are inherently capable of inducing cytopathic (toxic) effects and immune system responses [52].

At present, in the USA and EU countries, recommendations on medical and occupational protection when working with viral vector systems or gene therapy products under the conditions of pharmaceutical enterprises or laboratories and medical institutions are limited to general rules of biosafety when working with biological agents taking the levels of biological risk into account [13]. In the Russian Federation, due to the lack of wide industrial production of gene preparations, there are no coordinated and clear algorithms for assessing exposure to GTMP/ATMP/biotechnological components. In addition, the question of scientific justification for the principles of hygienic aerosol rationing of pharmaceutical components of GTMP/ATMP / biotechnological MPs for controlling the air of the production environment of enterprises or laboratories of the biotechnological industry remains open.

CONCLUSIONS

Our study outlines a number of aspects regarding the development of new-generation biological medicinal products (GTMP/ATMP/biotechnological medication) and associated risks of occupational exposure of workers in the conditions of pharmaceutical or laboratory production. The conducted literature review revealed that workers are exposed to the combined effect of adverse factors of production environment of a biological, physical, and chemical nature. There is a lack of information on the development of analytical methods for the identification of GTMP/ATMP components or biotechnological medications in the workplace air, wastewater, on working surfaces, etc. Only single reports were found in the available literature.

The conducted work allowed us to determine the key methodological approaches to assessing the potential industrial impact of GTMP, ATMP, and biotechnological medications on the employees of pharmaceutical companies. These include toxicological assessment of compounds with the establishment of possible toxicometry parameters; analysis of pharmacological and toxicokinetic features of the components of gene preparations; development of methods for their quantitative determination in different media; establishment of biomarkers of exposure and effect, with subsequent hygiene rationing and justification of key preventive measures.

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