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Review | Обзор

Quality control programmes for induced pluripotent stem cell-derived medicinal products

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ABSTRACT

INTRODUCTION. Currently, there are no harmonised regulatory requirements for the quality control of human somatic cell therapy and tissue-engineered medicinal products that contain differentiated cells derived from induced pluripotent stem cells (iPSCs). This lack of uniform requirements underscores the need for approaches to developing quality control programmes and establishing critical quality attributes for iPSC-derived medicinal products within the Eurasian Economic Union (EAEU) regulatory framework.

AIM. This study aimed to systematise global regulatory experience and EAEU regulatory requirements for the development and justification of quality control programmes for iPSC-derived medicinal products.

DISCUSSION. Medicinal products derived from iPSCs are mainly used in the treatment of neurodegenerative, cardiovascular, and oncological diseases, diabetes, graft-versus-host disease, and eye diseases. Over the past decade, specific recommendations and requirements for the quality of clinical-grade iPSCs have been published by the Chinese Society for Stem Cell Research (CSSCR), the Japanese Ministry of Health, Labour, and Welfare (MHLW), the Global Alliance for iPSC Therapy (GAiT), and the European Bank of iPSC (EBiSC). The EAEU regulatory requirements for the quality of genetically modified cells have been in effect since 2025 (Chapter 32 of Decision No. 89 of the Council of the Eurasian Economic Commission "On Approval of the Rules for Assessment of Biological Medicines in the EAEU" of November 3, 2016). The list of critical quality attributes for clinical-grade iPSCs proposed by the GAiT generally corresponds to the EAEU regulatory framework and can be used in drawing up quality control programmes for iPSC-derived medicinal products in the Russian Federation and the EAEU. Quality control programmes for finished somatic cell therapy or tissue-engineered medicinal products derived from iPSCs should be based on the principle of quality attribute traceability from the starting material onwards. The production of iPSCs is a full-fledged production process that must comply with Good Manufacturing Practice (GMP) requirements for genetically modified cells. Specific quality controls for iPSCs should include tests for residual reprogramming vector DNA, markers of the undifferentiated state, and pluripotency as part of purity characterisation, identification, and potency evaluation, respectively.

CONCLUSIONS. A quality control programme for a finished iPSC-derived medicinal product should correspond to the type of differentiated cells and take into account the indications for use. Critical quality considerations for iPSC characterisation include demonstrating the absence of contaminating undifferentiated cells or cells with new immunogenic epitopes and confirming the identity and genetic stability of iPSCs. The considered quality assessment approaches provide a basis for developing both quality control strategies for iPSC-derived medicinal products and specifications for marketing authorisation according to the EAEU requirements.

Keywords: induced pluripotent stem cells; cell therapy; somatic cell therapy medicinal product; tissue-engineered medicinal product; cell reprogramming; cell bank; quality control; quality attributes; regulatory authorities

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Программа контроля качества препаратов на основе индуцированных плюрипотентных стволовых клеток

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РЕЗЮМЕ

ВВЕДЕНИЕ. В настоящее время в регуляторной системе отсутствуют гармонизированные единые требования к контролю качества лекарственных препаратов (ЛП) на основе соматических клеток человека (соматотерапевтических ЛП) и тканеинженерных ЛП, в состав которых включены дифференцированные клетки, полученные из индуцированных плюрипотентных стволовых клеток (ИПСК). В связи с этим актуальным представляется формирование подходов в рамках регуляторной системы Евразийского экономического союза (ЕАЭС) к разработке программы контроля качества и установлению критических показателей качества ЛП, полученных из ИПСК.

ЦЕЛЬ. Систематизация опыта ведущих мировых регуляторных органов и нормативных требований Евразийского экономического союза для разработки и обоснования программы контроля качества лекарственных препаратов, полученных из индуцированных плюрипотентных стволовых клеток.

ОБСУЖДЕНИЕ. Основными направлениями терапевтического применения ЛП, полученных из ИПСК, являются лечение нейродегенеративных, сердечно-сосудистых, онкологических заболеваний, сахарного диабета, реакции «трансплантат против хозяина» и офтальмологической патологии. За последнее десятилетие рекомендации и требования к качеству ИПСК клинического уровня были представлены Китайским обществом исследований стволовых клеток, регуляторным органом Японии, Глобальным альянсом по терапии ИПСК (GAiT), Европейским банком ИПСК (EBiSC). В рамках ЕАЭС требования к качеству генетически модифицированных клеток введены в действие в 2025 г. (глава 32 Решения Совета Евразийской экономической комиссии от 03.11.2016 № 89 «Об утверждении Правил проведения исследований биологических лекарственных средств ЕАЭС»). Перечень критических показателей качества ИПСК клинического уровня, предложенный GAiT, в целом соответствует регуляторным нормам ЕАЭС и может быть использован при составлении программы контроля качества ЛП на основе ИПСК для применения на территории Российской Федерации и ЕАЭС. Программа

контроля качества готового соматотерапевтического или тканеинженерного ЛП, полученного из ИПСК, должна основываться на принципе прослеживаемости характеристик качества начиная с исходного материала. Процедура получения ИПСК является полноценным технологическим процессом, который должен соответствовать правилам надлежащей производственной практики (GMP) для генетически модифицированных клеток. Контроль качества ИПСК должен включать определение специфических показателей, включая следующие: остаточное содержание ДНК-векторов, использованных для перепрограммирования (оценка чистоты); экспрессия маркеров недифференцированного состояния клеток (подтверждение подлинности); тест на плюрипотентность (оценка активности).

ЗАКЛЮЧЕНИЕ. Программа контроля качества готовых ЛП, полученных из ИПСК, должна соответствовать типу дифференцированных клеток и учитывать показания к их клиническому применению. Критическими аспектами качества при характеризации ИПСК являются доказательство отсутствия примесных недифференцированных клеток и клеток с новыми иммуногенными эпитопами, подтверждение подлинности и генетической стабильности. Рассмотренные подходы к оценке качества ИПСК могут быть использованы для обоснования стратегии контроля качества ЛП на основе ИПСК, а также для формирования спецификаций при государственной регистрации по правилам ЕАЭС.

Ключевые слова: индуцированные плюрипотентные стволовые клетки; клеточная терапия; соматотерапевтический лекарственный препарат; тканеинженерный лекарственный препарат; перепрограммирование клеток; банк клеток; контроль качества; показатели качества; регуляторные органы

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INTRODUCTION

Cell therapy offers an innovative approach to treating severe, life-threatening, and socially significant diseases for which no effective, accessible pharmaceuticals are currently available. However, its application faces certain limitations. These arise from the inability to isolate specific cell types or failure to satisfy quality requirements for cells, primarily due to the presence of genome mutations, which prevents their use in manufacturing. To address these challenges, induced pluripotent stem cells (iPSCs) are being explored as a potential starting material. Recent research has been focused on obtaining iPSCs for clinical application (clinical-grade iPSCs) and establishing cell banks for subsequent production of cell therapy products [1–7]. The clinical applications of iPSCs and iPSC-derived specific differentiated cell types include neurodegenerative [8–11], cardiovascular [9, 12], oncological diseases [9, 13], diabetes [14, 15], graft-versus-host disease [16], and ocular diseases [9, 17].

Currently, the global regulatory system lacks harmonized, unified requirements for quality control of human somatic cell therapy products and tissue-engineered products containing differentiated cells derived from iPSCs. This can be attributed to several factors: a relatively recent discovery of the cell reprogramming mechanism, insufficient safety data for targeted modifications of the cell epigenetic profile, high cost of obtaining and certifying autologous iPSCs, limited characterization data on iPSCs during storage in cell banks (banking), as well as the absence of approved iPSC-based products and lack of established approaches to registration dossier assessment for marketing authorization. The Russian Federation lacks relevant experience with clinical-grade iPSCs, including their characterization, storage in cell culture collections, and established evaluation approaches.

The present paper aims to systematize the experience of leading global regulatory authorities as well as the regulatory requirements of the Eurasian Economic Union (EAEU) for the purpose

of development and justification of a quality control program for medicinal products derived from iPSCs.

To identify current clinical trials of iPSC-based products, we searched the ClinicalTrials.gov registry (using the keyword "induced pluripotent stem cell" and all clinical trial statuses except "unknown" and "withdrawn"). The search for scientific publications was conducted using the PubMed database and the following keywords: "induced pluripotent stem cell", "clinical-grade human induced pluripotent stem cell lines", "pluripotent stem cell-specific quality control".

MAIN PART

International approaches to quality control of induced pluripotent stem cells

At present, clinical trials of products derived from iPSCs are conducted mainly in the USA, China, and Japan (*Table S1*, published on the journal's website[1]).

It is important to note that all stem cell-based products in China, including those derived from iPSCs, are used as medical technologies without marketing authorization. The clinical trials conducted in China, as documented on the ClinicalTrials.gov website, are investigator-initiated trials (IIT), which are not conducted for the purpose of obtaining marketing authorization [18].

China

In 2021, the Chinese Society for Stem Cell Research published "Requirements for Human-Induced Pluripotent Stem Cells for Clinical Use". This document establishes key technical requirements, testing methods, and comprehensive instructions for the use, labeling, packaging, storage, and transportation of iPSCs during manufacturing and quality control *(Table 1)* [19].

Given the complexity of the iPSC manufacturing process, the use of allogeneic cells as a starting material offers an economically feasible solution for creating clinical-grade cell banks. Consequently, ensuring immunological compatibility is paramount. To reduce immunogenicity, the following approaches are used:

– deriving iPSCs from donors with homozygous major histocompatibility complex (MHC) haplotypes;
– modifying iPSCs to suppress human leukocyte antigens (HLA) expression, which helps overcome tissue mismatch between the donor and patient HLAs [2, 20].

Modified iPSC cell lines can be an optimal source for obtaining cell-based therapy products, offering a significant reduction in treatment wait times, eliminating the need to search for a suitable donor, and removing the requirement for prior immunosuppressive therapy. This approach proves to be a substantially more cost-effective treatment option compared to the use of autologous iPSCs [4].

The emergence of immunogenicity from iPSC-derived differentiated cells may be associated with the appearance of new immunogenic epitopes during the iPSC manufacturing stage due to spontaneous mutations arising in mitochondrial DNA during the cell reprogramming process. For this reason, genetic analysis is recommended at various stages of iPSC-based product manufacturing [9, 21].

Purity analysis (control of impurities) includes determining the residual content of DNA from transcription factors that may contribute to tumor formation. This risk is specific to iPSCs. It has been established that all four key Yamanaka reprogramming factors (Oct3/4, Sox2, Klf4, c-Myc) have tumorigenic potential. c-Myc is one of the most frequently mutated genes in cancer, and its mutations can act as driver mutations, providing a proliferative advantage and promoting selection of tumor cell clones [22].

J. Wu et al. [23] presented a quality control program and acceptance criteria to be used in iPSC manufacturing for all intermediate products used for generation of pancreatic islets for the treatment of patients with type 2 diabetes mellitus. The program includes quality control of the following cell types: endodermal stem cells, pancreatic progenitor cells, endocrine progenitor cells, and the actual islet cells (the active substance) (*Fig. S1*, published on the journal's website[2]).

The iPSCs were derived from peripheral blood mononuclear cells using a set of transcription factors (Oct4, Sox2, Klf4, c-Myc). Subsequently, two clones at passage 10 were selected, characterized, and used to obtain endodermal stem cells. At passage 20, the absence of known oncogenic mutations in the cells was confirmed using whole-genome sequencing. Genetic stability was

[1] https://doi.org/10.30895/2221-996X-2025-25-2-127-140-table-s1
[2] https://doi.org/10.30895/2221-996X-2025-25-2-127-140-fig-s1

Table 1. Quality control of induced pluripotent stem cells (iPSCs)
Таблица 1. Контроль качества индуцированных плюрипотентных стволовых клеток (ИПСК)

Attribute *Характеристика*	*Test methods* *Методы анализа*	*Requirements* *Нормы*
Identity: morphological analysis *Подлинность – морфологический анализ*	Microscopy *Микроскопия*	Cells grown in 2D conditions should form compact colonies with clear edges, be similar in morphology, and have a dense intercellular communication network *Клетки, культивированные в 2D-условиях, должны образовывать компактные колонии с четкими границами и характеризоваться схожей морфологией и наличием плотных межклеточных контактов*
Identity: karyotype *Подлинность – кариотип*	Differential G-banding *Дифференциальное G-окрашивание*	The normal karyotype is 46,XX or 46,XY *Нормальный кариотип 46,XX или 46,XY*
Viability *Жизнеспособность*	Haemocytometer counting with trypan blue staining *Подсчет клеток в гемоцитометре при окраске трипановым-синим*	Cell viability should be ⩾90% before cryopreservation and ⩾60% after cryopreservation, with cell counting in two runs, followed by the calculation of the mean value. The difference between the calculation results should not exceed 10% of their arithmetic mean *Жизнеспособность клеток ⩾90% до криоконсервации и ⩾60% после криоконсервации при подсчете в двух повторах с последующим расчетом среднего значения. Разница между результатами подсчетов не должна превышать 10% от среднего арифметического*
Identity: cell surface markers *Подлинность – маркеры клеточной популяции*	Flow cytometry *Проточная цитометрия*	The expression of at least two of the surface cell markers SSEA3, SSEA4, TRA-1-60 and TRA-1-81 in the cell population should be ⩾70%, and the expression of the intracellular markers Oct4 and Nanog should be ⩾70% *Уровень экспрессии, по крайней мере, двух поверхностных клеточных маркеров (SSEA3, SSEA4, TRA-1-60, TRA-1-81) в популяции клеток должен составлять ⩾70%, уровень экспрессии внутриклеточных маркеров Oct4 и Nanog должен составлять ⩾70%*
Purity: residual amounts of transcription factor DNA *Чистота – остаточное содержание ДНК транскрипционных факторов*	Quantitative PCR analysis *Количественный ПЦР-анализ*	The concentration of target genes is calculated according to the standard curve plotted using reference standards for the DNA of target genes *Расчет концентрации целевых генов производится в соответствии с построенной стандартной кривой при использовании эталонных стандартов ДНК целевых генов*
Pluripotency test *Тест на плюрипотентность*	*In vivo* teratoma formation in immunodeficient mice *Формирование тератомы in vivo на иммунодефицитных мышах*	iPSCs should be able to form *in vivo* teratomas with derivatives of all three germ layers after administration of iPSCs (subcutaneous, intramuscular, into the space of the seminal tubules under the testicular membrane, or under the renal capsule), followed by histological examination with haematoxylin and eosin staining (6–10 weeks after teratoma formation) *ИПСК должны быть способны образовывать in vivo тератомы с производными всех трех зародышевых листков после введения клеток (подкожно, внутримышечно, в пространство семенных канальцев под оболочкой яичек или под почечной капсулой) с последующим гистологическим исследованием при окрашивании препарата гематоксилином и эозином (через 6–10 нед. после образования тератом)*
Sterility Mycoplasma Adventitious agents *Стерильность* *Микоплазма* *Занесенные агенты*	Compendial methods *Фармакопейные методы*	The donor material should be checked for the presence of human immunodeficiency virus, hepatitis B and hepatitis C viruses, human T-lymphotropic virus, Epstein–Barr virus, cytomegalovirus and Treponema pallidum agent at the screening stage of donors. Cells should be sterile and free of bacteria, fungi, mycoplasmas, and viruses *Проверка донорского материала на наличие вируса иммунодефицита человека, вирусов гепатита B и гепатита C, Т-лимфотропного вируса человека, вируса Эпштейн–Барр, цитомегаловируса и возбудителя сифилиса осуществляется на стадии скрининга доноров. Клетки должны быть стерильными, не содержать бактерий, грибов, микоплазм, вирусов*
Authentication (in-process control) *Аутентификация (внутрипроизводственный контроль)*	Short tandem repeat analysis *Метод коротких тандемных повторов*	STR profiles of iPSCs and donor material should correspond to each other *Соответствие STR-профилей ИПСК и материала донора*

The table is prepared by the authors using data from [19] / Таблица составлена авторами по данным [19]

Note. PCR, polymerase chain reaction; STR, short tandem repeat
Примечание. ПЦР – полимеразная цепная реакция; STR – метод коротких тандемных повторов.

assessed via karyotyping. Safety in terms of the absence of iPSC impurities was evaluated in animal models of teratoma. Products obtained at intermediate manufacturing stages – pancreatic progenitor cells and endocrine progenitor cells – were subjected to reduced quality control, assessing identity and the absence of microorganisms (sterility, mycoplasmas, adventitious agents, and endotoxins). The active substance (islet cells) underwent comprehensive characterization using the following parameters: identity (determination of the main target and non-target cell types); potency – assessed by measuring insulin (C-peptide) secretion following glucose stimulation; and the absence of microorganisms.

Japan

In Japan, research (Investigator-Initiated Trial stage) is being conducted on medicinal products derived from iPSCs for the treatment of various diseases: retinitis pigmentosa (jRCTa050200027), Leber congenital amaurosis (jRCTa050210178, jRCTa050200122, jRCTa050190084), oncological diseases (jRCTa030220741), cardiovascular diseases (jRCTa032200189), knee cartilage injuries (jRCTa050190104), and spinal cord injuries (jRCTa031190228) [24]. In 2013, Japan issued a guideline for quality control and preclinical studies required for the clinical application of retinal pigment epithelial cells derived from iPSCs. The guideline outlined the following product indications: age-related macular degeneration, degenerative myopia, Stargardt disease, traumatic injuries, and retinitis pigmentosa[3].

The guideline presents cell quality requirements primarily related to efficacy and specific safety (i.e., impurities control), and also describes the quality attributes, methods, and markers *(Fig. 1)*.

Critical quality attributes for clinical-grade induced pluripotent stem cells

In 2018, the Global Alliance for iPSC Therapies (GAiT [20]) defined a minimum set of quality control criteria and critical quality attributes for clinical-grade iPSCs intended for use as starting material for the production of cell therapy products to be banked [1]. These recommendations were developed based on a thorough analysis of quality attributes as factors contributing to potential risks in iPSC clinical use. They also aim to foster a better understanding of the possible consequences that may arise during testing (*Table S2*, published on the journal's website[4], [25–29]).

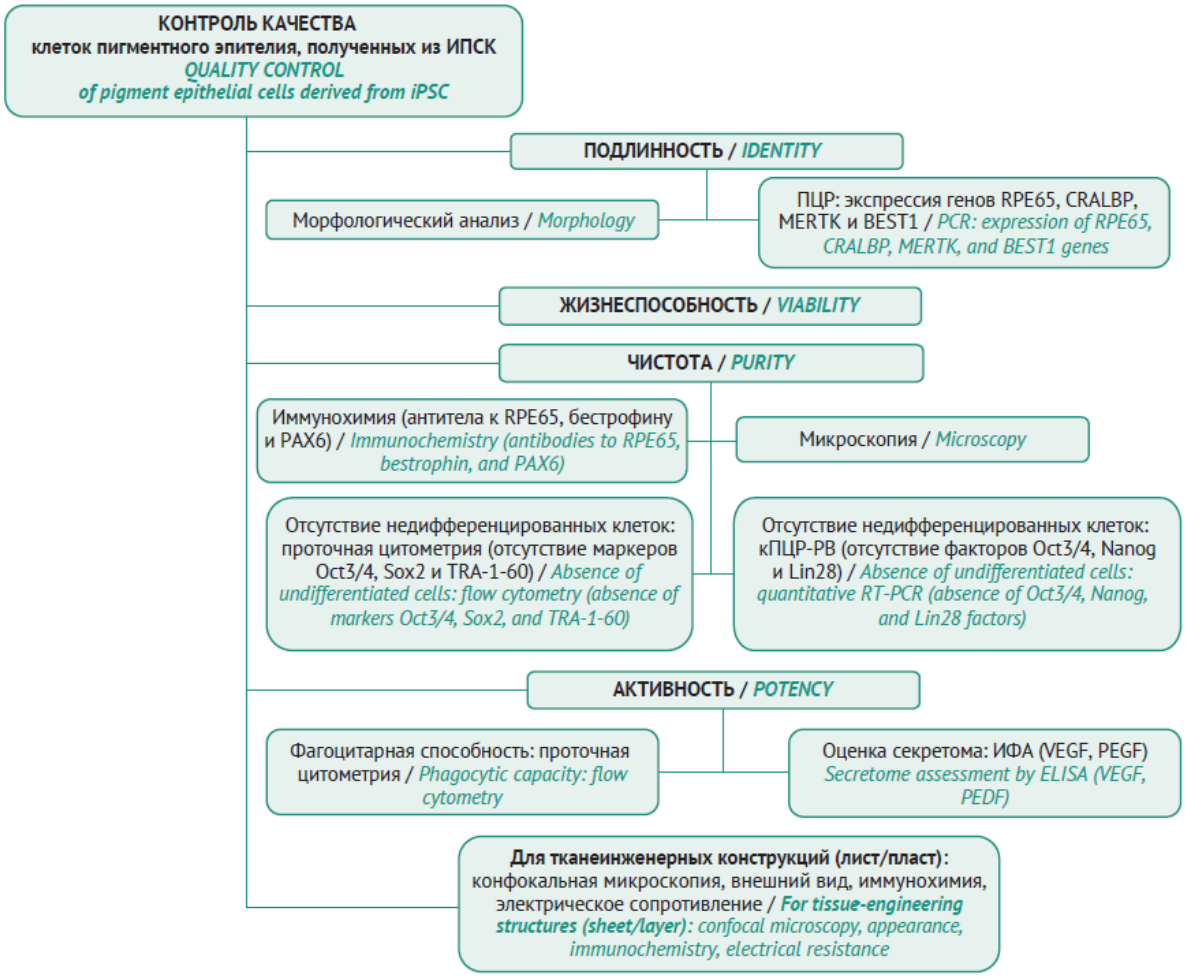
To address the assessment of iPSC quality attributes, *Table S2* has been supplemented with references to the current pharmacopoeial monographs of the State Pharmacopoeia of the Russian Federation and the EAEU Pharmacopoeia, as well as to other regulatory sources stipulating the use of non-compendial methods.

Additionally, intermediate stages of iPSC manufacturing may employ an expanded range of characterization and testing methods, including the following:

- detailed description of cultivation conditions and determination of iPSC proliferative activity;
- genetic stability testing methods that account for the increased risk of mutation formation due to cell reprogramming processes, for example: single nucleotide polymorphism (SNP) analysis, which allows detection of subchromosomal changes and neutral loss of heterozygosity, potentially indicating cell transformation; whole-genome/exome sequencing to identify loci of potential complete/partial integration of reprogramming vectors (associated with tumorigenic risk) and other genetic markers in accordance with the international Catalogue Of Somatic Mutations In Cancer (COSMIC) database[5], which contains information on known oncogenes and tumor suppressor genes classified according to the recommendations of the American College of Medical Genetics and Genomics (ACMG) [30];
- immunocytochemical determination of markers specific to human pluripotent stem cells;
- gene expression analysis using molecular arrays, mRNA arrays, or RNA sequencing, which allows for the prediction of functional pluripotency.

Subsequently, the quality control strategy proposed by GAiT for characterizing clinical-grade iPSCs for inclusion in cell collections/banks was adapted by the European Bank for Induced Pluripotent Stem Cells (EBiSC) [7], as well as by some medical centers specializing in the

[3] Guidance on Evaluation of Autologous Induced Pluripotent Stem Cells-derived Retinal Pigment Epithelial Cells. Pharmaceutical and Food Safety Bureau. Ministry of Health, Labour and Welfare. Japan; 2013.
[4] https://doi.org/10.30895/2221-996X-2025-25-2-127-140-table-s2
[5] COSMIC. Catalogue of somatic mutations in cancer. https://cancer.sanger.ac.uk/cosmic



The figure was prepared by the authors using materials of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Japan[6] / Рисунок подготовлен авторами по материалам Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Japan[6]

Fig. 1. Quality attributes for pigment epithelial cells derived from induced pluripotent stem cells (iPSCs), as listed in the requirements of the Japanese regulatory authorities.

Рис. 1. Необходимый перечень показателей качества для клеток пигментного эпителия, полученных из индуцированных плюрипотентных стволовых клеток (ИПСК) согласно требованиям регуляторных органов Японии.

Note. RT-PCR, real-time polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; VEGF, vascular endothelial growth factor; PEDF, pigment epithelium-derived factor.

Примечание. кПЦР-РВ — количественная полимеразная цепная реакция в реальном времени; ИФА — иммуноферментный анализ; VEGF — фактор роста эндотелия сосудов; PEDF — фактор пигментного эпителия.

production of gene and cell therapy products in compliance with Good Manufacturing Practice (GMP) requirements [4, 5, 31].

To standardize the process, EBiSC has proposed recommendations for characterizing iPSCs when establishing clinical-grade cell banks [7]. These recommendations require safety assessments on primary cells, early passages of the cell line after reprogramming, and the iPSC cell line intended for banking. The assessment is performed using the following methods: cell line authentication (short tandem repeat profile), analysis of genetic stability (G-banding, SNP analysis, or comparative genomic hybridization), and sterility and mycoplasma testing. The proposed quality control approach for donor material and iPSC production intermediates helps to accumulate a reliable body of historical data. This data is essential for justifying the scope of current quality control (for example, viral safety testing of the derived cell lines is conducted only in the absence of donor test results)

[6] Guidance on Evaluation of Autologous Induced Pluripotent Stem Cells-derived Retinal Pigment Epithelial Cells. Pharmaceutical and Food Safety Bureau. Ministry of Health, Labour and Welfare. Japan; 2013.

and for evaluating any changes in the manufacturing process. For direct cell reprogramming, it is recommended to test the collected primary samples and/or the derived cell populations for sterility and viral agents, as well as to confirm cell line identity (i.e., its belonging to a specific individual).

The availability of genetic testing results for primary cells (e.g., karyotype, SNP profile) subsequently enables the identification of congenital genetic anomalies and any deviations arising directly during reprogramming.

It is recommended to confirm iPSC identity, potency, and purity on the cells intended for banking and prior to obtaining differentiated cells for the finished medicinal product. This involves quantitative determination of viable cells, assessment of undifferentiated iPSC markers expression, and pluripotency assays, in addition to other relevant tests. Morphological analysis is recommended for all materials during iPSC manufacturing, including primary cells and throughout routine cultivation, as cell morphology is highly susceptible to changes, e.g. from microbial contamination or genetic mutations.

For routine cultivation monitoring, the following conditions and time intervals are recommended:

- STR profile determination: every 6–8 weeks or 10–12 passages for cell lines in culture;
- genetic stability assessment: every 6 weeks or 10 passages, with additional assessments performed following selection, or if changes in cell morphology and growth rate are observed in culture;
- sterility check: daily;
- mycoplasma testing: every 3–4 weeks or 5–6 passages, and if changes in cell morphology and growth rate are observed in culture;
- morphology assessment: daily;
- determination of specific marker expression and pluripotency test: if changes in cell morphology and growth rate are observed in culture.

According to J.J. Novoa et al. [4, 5], the proposed quality control strategy [1] allows for characterization of iPSCs in terms of the required safety and efficacy attributes for their subsequent storage in cell banks. The authors validated quality control methods specific to iPSCs for determining:

- residues of DNA vectors used for reprogramming (purity assessment);
- markers of undifferentiated cells (identity confirmation);
- pluripotency (potency assessment).

A key stage in iPSC in-process control is safety assessment, which includes evaluation of the tumorigenic potential [4, 5]. This involves assessment of the residual content of DNA vectors used for reprogramming and determination of the optimal minimum number of cell line passages. These steps are essential for assessing cell genome stability for subsequent iPSC banking and clinical use. J.J. Novoa et al. [4, 5] demonstrated that screening for the presence of residual episomal DNA vectors is most appropriate between the eighth and tenth passages. This approach offers a threefold benefit: excludes cell lines containing episomal vectors, optimizes the number of passages to mitigate risks for genome integrity, and minimizes the number of discarded iPSC cell lines.

A minimum sample size of 20,000 cells (120 ng of genomic DNA) was established for the analysis of DNA vectors. Since the DNA vectors used contain the Epstein–Barr virus (EBV) regulatory element EBNA-1, additional donor testing for EBV infection and corresponding antibodies is necessary. If the test returns positive, further examination of the donor material is necessary to detect the EBV BNRF1 marker. This approach helps to differentiate endogenous EBV infection from the EBNA-1 element introduced during iPSC reprogramming. Additionally, whole-genome sequencing is recommended for iPSC cell lines intended for cell bank storage. This helps to identify potential integration of plasmid sequence fragments lacking the EBNA-1 sequence [5].

The iPSC potential to differentiate into three germ layers is assessed through a functional pluripotency test. The test is performed using cover slips and confocal microscopy, enabling morphological analysis and evaluation of lineage-specific marker expression. The iPSC lines generated by J.J. Novoa et al. [4] demonstrated the ability to differentiate into all lineages: pancreatic islets (endoderm); renal organoids and cardiomyocytes (mesoderm); keratinocytes, GABAergic interneurons, and inner ear structures (ectoderm). To evaluate the expression of undifferentiated state markers, three types of markers were used: two extracellular (SSEA4 and TRA-1-60) and one intracellular (Oct3/4) [5].

Eurasian Economic Union regulatory requirements for the quality control of induced pluripotent stem cells

Starting Materials and Reagents

The quality control of medicinal products derived from iPSCs is supported by a regulatory and legal framework throughout their entire lifecycle, starting from the development stage, in strict compliance with the EAEU regulations[7]. In 2025, detailed requirements for the development, quality control, and conduct of preclinical and clinical studies of medicinal products based on somatic and genetically modified (GM) cells were approved as chapters 31 and 32 of the Annex to Decision No. 89 of the Council of the Eurasian Economic Commission (EEC)[8] (hereinafter, EEC Council Decision No. 89). These provisions are fully harmonized with European requirements[9]. The requirements specify that GM cells are developed for therapeutic use (Advanced Therapy Medicinal Products, ATMPs) or for manufacturing of cell therapy or tissue-engineered products (e.g., for producing iPSCs which are subsequently differentiated into somatic cell therapy or tissue-engineered products). For iPSC-based products, GMP principles and science-based recommendations are applied consistently starting from the cell collection stage, including iPSC generation and subsequent selection steps. The quality control program for such products must cover all manufacturing stages: control of raw materials, iPSCs, intermediate products, active pharmaceutical ingredient (API), and the finished product.

The generation of iPSCs involves the use of the following starting components: factors ensuring cell modification (reprogramming); factor delivery vehicles (plasmid/viral vectors, etc.); human primary cells.

Quality control of iPSC generation includes the following key aspects:

- verification of modification factor combinations (including commercially available kits). Before use, factors must undergo sterilization and testing for viral contamination, including replication-competent viruses when viral vectors are used as delivery vehicles;
- characterization of primary cells and GM cells (iPSCs) in terms of: cell viability, concentration, purity (residual contents of transcription factor DNA, other impurities), sterility, potency (pluripotency assay). The identity (identification) must be confirmed using appropriate genotypic and/or phenotypic markers. These parameters align with the critical quality attributes for clinical-grade iPSCs when used as a starting material for cell therapy products, as proposed by GAiT [1];
- the Master Bank of GM cells (iPSCs) must be established before initiation of Phase I clinical trials (as stipulated by Chapter 1 of EEC Council Decision No. 89);
- safety assessment of starting materials (donor material, iPSCs) for potential presence of adventitious agents, and confirmation of genetic stability;
- cell characterization (iPSCs, iPSC-based products) before and after genetic modification, as well as after cryopreservation (freezing and storage).

Cell Banks Characterization

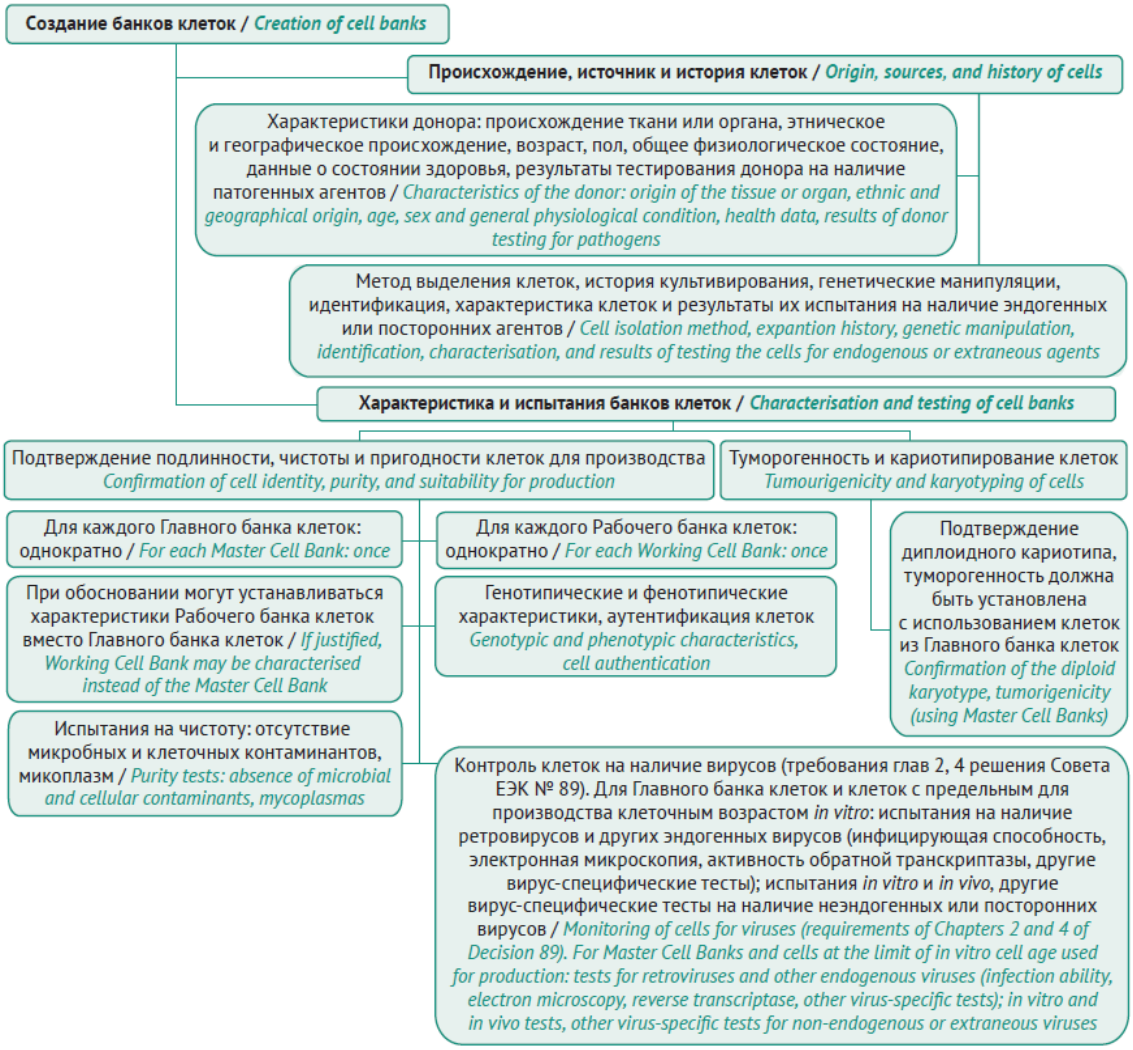
General requirements for cell bank characterization, as detailed in Chapter 1 of EEC Council Decision No. 89 and illustrated in *Figure 2*, can be applied to iPSC bank characterization. However, the latter requires additional assessment of genetic stability and conducting whole-genome or whole-exome sequencing to identify mutations. To justify the use of specific types of differentiated cells, the pluripotent cell state must first be confirmed. A crucial element is verification of iPSC genetic stability, as this is fundamental for establishing the limit of *in vitro* cell age for manufacturing. This stability can be assessed through examination of morphological characteristics, cell growth parameters, and biochemical, immunological, genotypic, and phenotypic markers.

Since a GM cell (iPSC) bank is established after the cells are obtained from somatic cells

[7] Decision No. 89 of the Council of Eurasian Economic Commission dated 3 November 2016 On Approval of the Rules for Conducting Research on Biological Medicinal Products in the Eurasian Economic Union.
Decision No. 78 of the Council of Eurasian Economic Commission dated 3 November 2016 On the Rules of Registration and Examination of Medicines for Human Use.

[8] Decision No. 13 of the Council of Eurasian Economic Commission dated 22 January 2016 On Amendments to the Rules for Conducting Research on Biological Medicinal Products in the Eurasian Economic Union.

[9] Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006). EMEA; 2008.
Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells. (EMA/CAT/GTWP/671639/2008). EMEA; 2020.



The figure was prepared by the authors using Decision No. 89 of the Council of the Eurasian Economic Commission / Рисунок подготовлен авторами по данным Решения Совета ЕЭК № 89

Fig. 2. General aspects of cell bank characterisation.

Рис. 2. Общие аспекты характеризации банков клеток.

through genetic modification, it is essential to establish a comprehensive list of attributes for the finished product. This list should include assessment of impurities characteristic of a specific manufacturing process. Special attention must be given to determining residues of reprogramming factor DNA and their delivery vehicles, such as plasmids, viral vectors, etc.

Registration Dossier Materials

Pursuant to Chapter 14 of EEC Council Decision No. 89 (clinical trial requirements) and EEC Council Decision No. 78 (Module 3 requirements), a submission must include a description of the manufacturing process for biological medicinal products (including iPSC-based products). This description must include details of critical stages, quality attribute limits and ranges, identification of critical parameters affecting key characteristics (identity, purity, potency, count, stability), and the results of process validation. Data may be incomplete in the case of Phase I-II clinical trials[10].

[10] Decision No. 89 of the Council of Eurasian Economic Commission dated 3 November 2016 On Approval of the Rules for Conducting Research on Biological Medicinal Products in the Eurasian Economic Union.
Decision No. 78 of the Council of Eurasian Economic Commission dated 3 November 2016 On the Rules of Registration and Examination of Medicines for Human Use.

Results of comparability studies for the medicinal product are required, for example, following changes in the cellular starting material (e.g., cell source, isolation method for specific cell subpopulation(s), introduction of a cell material freezing stage, etc.) or to the API or finished product manufacturing process.

The documentation for the finished iPSC-based product must contain a detailed rationale for all quality attributes included in the specifications for both the API and the finished product. This must cover the acceptance criteria (permissible values) for product purity, impurity residues (with maximum allowable levels based on clinical safety), potency, and other critical quality parameters affecting the product's functional characteristics.

The relevance and suitability of analytical quality control methods are paramount. Submissions for Phase I clinical trials must include established acceptance limits and validation parameters in a tabulated form. For Phase II–III clinical trials, a summary of the validation results must be submitted. Marketing authorisation submissions require a complete data package on validation of quality control methods[11].

In the case of iPSC-based products, stability study results, information on the proposed shelf life and storage conditions, must be presented separately for the API, the finished product, and any intermediate products requiring long-term storage during manufacturing. Critical quality attributes for medicinal product stability studies must include identity, potency, and count. To obtain permission for clinical trials, a submission must include stability data for at least one batch produced using the manufacturing process intended for the production of clinical trial batches. Stability data from batches produced during development or using a prior manufacturing process is acceptable, provided the quality of such batches is equivalent to that of the product to be used in the clinical trial.

The quality control program and specifications for an iPSC-based product must address the following aspects, in accordance with clause 17.3 of EEC Council Decision No. 78 on special requirements for Module 3 of the registration dossier for somatic cell therapy products and medicinal products based on GM cells:

- Module 3 of the registration dossier must contain a summary of the procurement, collection, and testing of human tissues and cells (including starting materials used to generate iPSCs);
- if allogeneic cells are pooled after iPSC differentiation, a pooling strategy must be presented, along with information on measures to ensure traceability (as pooling of iPSCs has not been done so far due to the increased risk of genetic instability);
- to predict therapeutic application and assess potency, it is crucial to consider the variability of starting materials and the origin of primary cells. This is due to the known "epigenetic memory" of iPSCs [32, 33]. For example, it has been demonstrated that iPSCs derived from fetal neural stem cells generated a greater number of neural progenitors and differentiated neuronal cells compared to fibroblast-derived iPSCs [34]; iPSCs derived from keratinocytes more frequently formed neuroectodermal structures compared to fibroblast-derived iPSCs [35];
- it is essential to provide data on the validation of the manufacturing process and quality control methods, along with a description and qualification of iPSC cell banks;
- quality control of the finished iPSC-based somatic cell therapy products must include the following parameters: identity, purity (sterility, mycoplasmas, endotoxins, adventitious agents, and cellular contaminants), viability, potency, karyological profile, tumorigenicity, suitability for the intended medical use, confirmation of genetic stability, process- and product-related impurities. Particular attention is paid to the presence of residues of undifferentiated iPSCs, cells with new immunogenic epitopes, and other intermediate products arising during reprogramming, cultivation, and other manufacturing stages. It should be noted that a major challenge in characterizing the identity and potency of iPSC-derived cells, is their insufficient maturation;
- justifications must be provided for the use of in-process control data for batch release;
- the influence of biologically active molecules (growth factors, cytokines) on other API components must be described;

[11] Decision No. 89 of the Council of Eurasian Economic Commission dated 3 November 2016 On Approval of the Rules for Conducting Research on Biological Medicinal Products in the Eurasian Economic Union.

– for products with three-dimensional structures, it is necessary to assess the differentiation state, structural and functional organization of cells resulting from combination with matrices, scaffolds, medical devices, and the resulting extracellular matrix;
– the description of product development must include an analysis of cell population integrity after technological manipulations with the finished medicinal product.

Thus, the quality control program for a finished somatic cell therapy or tissue-engineered product derived from iPSCs must be based on the principle of traceability of quality attributes starting from the raw material.

CONCLUSIONS

Global regulatory authorities, international organizations, including the European Bank for Induced Pluripotent Stem Cells (EBiSC), and individual medical centers specializing in the manufacturing of gene and cell therapy products, whose approaches were reviewed in this paper, all mandate strict quality traceability for iPSC-based products, starting from the raw material. This requirement stems from the specific nature of their manufacturing, which is recognized as a comprehensive technological process subject to GMP regulations for genetically modified cells.

Quality control of iPSCs requires determination of specific parameters, including residues of DNA vectors used for reprogramming (purity assessment); expression of undifferentiated cell markers (identity confirmation); and a pluripotency test (potency assessment). However, current regulations lack sufficient detail regarding the qualification and validation procedures for these methods, including acceptance criteria, which could be used in GMP manufacturing environments.

The list of critical quality attributes for clinical-grade iPSCs, as proposed by the Global Alliance for iPSC Therapies (GAiT), generally aligns with the EAEU regulations. With due regard for the regulatory and methodological documents, as well as scientific recommendations presented in this review, this list can serve as a basis for developing quality control programs for iPSC-based products intended for use in the Russian Federation and the EAEU.

The quality control program for finished somatic cell therapy or tissue-engineered products derived from iPSCs must be appropriate to the type of differentiated cells and consider the indications for clinical use. Critical quality aspects in characterizing iPSCs include demonstrating the absence of contaminating undifferentiated cells and cells with new immunogenic epitopes, as well as confirming identity and genetic stability.

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Authors' contributions. All the authors confirm that they meet the ICMJE criteria for authorship. The most significant contributions were as follows. ***E.V. Melnikova*** conceptualised the study, drafted the manuscript, and formulated the conclusions. ***O.A. Rachinskaya*** and ***I.S Semenova*** worked with literature sources. ***V.A. Merkulov*** participated in formulating the conclusions and approved the final version of the manuscript for publication.

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