

Review of international and national principles of law in the field of tissue and cell transplantation and the approaches of improving the regulatory framework of hematopoietic stem cells transplantation in Ukraine



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ABSTRACT

The article analyses modern international and national laws in the field of tissue and cell transplantation. The peculiarities of regulation of hematopoietic stem cell transplantation (HSCT) in the European Union, USA, Canada, Australia, as well as in Ukraine are considered in detail. Attention is focused on the analysis of general principles of regulation and practical aspects related to harmonization of legislation, standards and practical guides of different countries in the field of HSCT with current unified international standards. These standards should facilitate interstate exchange of quality and safe transplants of hematopoietic stem cells and improve accessibility of this treatment in Ukraine and in the world. The problems and disadvantages of the domestic legislation concerning regulatory support in the field of HSCT are shown. The proposals on improvement of the legal framework efficiency in the field of HSCT in Ukraine are presented.

KEY WORDS: hematopoietic stem cells; hematopoietic stem cell transplantation; regulatory and legal frameworks of stem cell transplantation

Nowadays in the world, transplantation develops in three directions – transplantation of organs, tissues and cells. The latter option includes, in particular, hematopoietic stem (progenitor) cells transplantation (HSCT). The above directions have both general features and their basic features of medical, infrastructural, organizational and regulatory nature. At present, there is a need for a comprehensive analysis of regulatory issues that may affect the development of HSCT system in Ukraine. The study of international and advanced national legal regulations in the field of HSCT can help in choosing the best solutions for the development of relevant regulatory documents in our country. Leading positions in the development and implementation of such documents belong to the countries of the European Union (EU), USA, Canada, Australia and others.

It is relevant to conduct a comparative analysis of international and national regulations in the field of HSCT in order to identify common features and differences with the relevant regulatory documents in Ukraine. This will allow to identify disadvantages and make proposals for further

improvement and efficiency of Ukraine's regulatory framework in the field of HSCT taking into account the provisions of international and advanced national regulatory documents.

ANALYSIS OF INTERNATIONAL AND NATIONAL LEGAL REGULATION IN THE FIELD OF TRANSPLANTATION OF TISSUES AND CELLS, INCLUDING HSCT

Up-to-date transplantation of organs, tissues and cells is based on a number of general principles that can be considered as global standards. The World Health Organization (WHO) is the governing and coordinating agency for health care within the United Nations system. In 1991, resolution WHA44.25 of the World Health Assembly first adopted Guiding principles (GP) on human organ transplantation. This document included nine provisions [1].

The above principles were revised and supplemented alongside the changes in the field of transplantation. WHO paid particular attention to

the transplantation of human cells and tissues in the updating GP. Normative requirements for the transplantation of human cells and tissues have been widely discussed at two global consultations held under the aegis of WHO in 2004 and 2006 [2-4].

The latest edition of the WHO Guiding principles on human organ transplantation were approved on May 21, 2010 at the 63rd Session of the World Health Assembly by resolution WHA63.22. This document includes eleven GPs, which represent an ordered, systematic, structural framework for the creation of mechanisms for the donation, distribution and transplantation of human cells, tissues and organs for medical treatment observing ethical principles. These principles do not apply to transplantation of embryonic or reproductive cells, reproductive tissues, as well as blood and blood components for transfusion [5, 6]. GP had a great influence on the formation of an international legal framework in the field of donation and transplantation of cells, tissues and organs, and formed the basis of the legislation of WHO member countries.

According to GP No. 1, cells, tissues and organs (CTOs) may be removed from the bodies of deceased persons for the purpose of transplantation if (a) any consent required by law is obtained, and (b) there is no reason to believe that the deceased person objected to such removal [5].

According to GP No. 2, physicians determining that a potential donor has died should not be directly involved in cell, tissue or organ removal from the donor or subsequent transplantation procedures; nor should they be responsible for the care of any intended recipient of such cells, tissues and organs [5].

GP No. 3 deals with lifetime donation, namely, the possibility of retrieval CTOs in adults and competent persons who are in a genetic, legal or emotional relationship with their recipient. An obligatory condition of a lifetime donation is a voluntary informed consent of a capable donor, obtained free of any undue influence or coercion, provided that the person is informed in a complete and understandable fashion about possible risks, ensuring the scrupulously applied of selection criteria, proper professional care and a subsequent (after donation) monitoring [5].

GP No. 4 recommends prohibiting the removal of CTOs from living minors or incapacitated donors, with narrow exceptions allowed under national law. The commentary to the above principle explains that the main exceptions may be made for family donation of regenerating cells (when a therapeutically comparable adult donor is not available) and kidney transplantation from the identical twins (no need for immunosuppressive therapy in the recipient) [5].

GP No. 5 recommends prohibiting the sale and purchase of CTOs. Their donation is possible only free of charge, without any payment or other reward of monetary value. It is necessary to prohibit the purchase or offer for the purchase of CTOs, or their sale by a living donor or the closest relatives of the deceased. However, this principle does not exclude the reimbursement of reasonable and duplicate expenses incurred by the donor, including paying the costs of recovering, processing, preserving and supplying human cells, tissues or organs for transplantation [5].

GP No. 6 recommends promoting altruistic donation by means of advertisement or public appeal. These measures may be carried out in accordance with the rules and regulations in force in a particular country. However, advertising should be prohibited for the needs of the CTOs or their availability for offering a payment or in order to find funds to pay individuals for their CTOs, or the closest relatives (in the case of a deceased donor). It is also necessary to prohibit brokering for involving payments to such persons or a third party [5].

GP No. 7 recommends that physicians and other health care professionals do not engage in transplantation procedures. Health insurers and other potential payers should bear the costs associated with it, in cases when organ for transplantation have been obtained through exploitation or coercion of, or payment to, the living donor, or the next of kin of a deceased donor [5].

GP No. 8 recommends that all health-care facilities and professionals involved in procurement and transplantation procedures should be prohibited from receiving any payment that exceeds the justifiable fee for the services rendered [5].

GP No. 9 recommends that allocation of CTOs should be guided by clinical criteria and ethical norms, not financial or other considerations. Allocation rules, defined by appropriately constituted committees, should be equitable, externally justified and transparent [5].

GP No. 10 recommends the use of high quality, safe and efficacious procedures that are essential for both donors and recipients. Both the living donor and the recipient should evaluate the long-term outcomes of donation the CTOs and their transplantation in order to document the benefits and harm. The level of safety, efficiency and quality of human CTOs for transplantation, which is a health product of such an exceptional nature, must be maintained and optimized on an ongoing basis. To this end, quality systems should be applied, including aspects such as traceability and vigilance, reporting adverse events or reactions, both nationally and for exported human products [5].

GP No. 11 recommends that organization and execution of donation and transplantation activities, as well as their clinical results, must be transparent and open to scrutiny, while ensuring that the personal anonymity and privacy of donors and recipients are always protected.

Briefly, the essence of the above-mentioned WHO GPs can be formulated as follows:

- 1) agreement of the deceased person on the donation;
- 2) absence of conflict of interests in determining the death of a donor;
- 3) consent of a living person for donation;
- 4) protection of minors and incapacitated persons;
- 5) prohibition of the sale or purchase of transplants;
- 6) propaganda of free donation, the prohibition of advertising and brokering for the purchase and sale of grafts;
- 7) prohibition of participation in unfair transplantations;
- 8) the relevance of professional services and reimbursement;
- 9) distribution rules;
- 10) quality, safety, efficacy of procedures and transplantation;
- 11) transparency and confidentiality.

The WHO GPs No. 1 and 2 are not directly related to the HSCT, since they provide recommendations on the main conditions for the removal of CTOs from deceased persons. Other GPs are related to HSCT, as they can be applied to lifetime donations. WHO GP No. 8 strengthens GPs No. 5 and No. 7, prohibiting the removal and use of CTOs for profit.

The very successful international transplant documents are the standards developed within the framework of the Council of Europe (CE). They are Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, 4.IV.1997 (Convention) and Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin, 24.I.2002 (Additional Protocol) [8]. The legal norms of the «Convention» are based on the Universal Declaration of Human Rights of the UN and the Convention for the Protection of Human Rights and Fundamental Freedoms of the CE, ratified by Ukraine in 1997, as well as other regulations [9-11].

Let us consider how the main provisions of WHO GP, which can be applied to HSCT, are reflected in the above-mentioned documents of the CE and other legislation. Similar to WHO GP No. 3 requirements for adult capable persons are in Chapter VI, «Organ and tissue removal from living donors for transplantation purposes» of Convention and Chapter III, «Organ and tissue removal from living persons» of Additional Protocol. They are Article 19 – General rule of the Convention and Article 9 – General rule, Article 10 – Potential organ donors, Article 11 – Evaluation of risks for the donor, Article 12 – Information for the donor, Article 13 – Consent of the living donor, Article 15 – Cell removal from a living donor, Article 7 – Medical follow-up of Additional Protocol [5, 7, 8].

The general rules state that removal of organs and tissues from a living person can only be performed for the treatment of the recipient and in the absence of the necessary organ or tissue of a deceased person and another alternative method of treatment of comparable efficacy. Any intervention in the field of health may be carried out only after the volunteer and informed consent of the person concerned, which must be provided

clearly and specifically, in writing or before an appropriate official body. Such person is provided in advance with relevant information about the purpose and nature of the intervention, as well as about its consequences and risks. The concerned person can freely withdraw his consent at any time. This applies to both the donor and the recipient. Art. 13 of the Additional Protocol in compliance with the provisions of Art. 14 and 15, which will be listed below, provides that an organ or tissue can be removed from a living donor only after the person concerned has given a free, informed and specific consent to this in writing or before an official body. The person concerned may freely withdraw consent at any time.

Article 20 «Protection of persons not able to consent to organ removal» of Convention and Article 14 «Protection of persons not able to consent to organ or tissue removal» prohibits the removal of transplants from minors and persons who are incapacitated, but in exceptional cases. Unlike the commentary to WHO GP No. 4, these documents provide for only one exception – to remove regenerative tissues. In particular, paragraph 2 of Art. 14 in Additional Protocol provides the removal of regenerative tissue from such a person if the following conditions are met:

- i) there is no compatible donor available who has the capacity to consent;
- ii) the recipient is a brother or sister of the donor;
- iii) the donation has the potential to be life-saving for the recipient;
- iv) the authorisation of his or her representative or an authority or a person or body provided for by law has been given specifically and in writing and with the approval of the competent body;
- v) the concerned potential donor does not object [5, 7, 8].

According to Art. 15 Additional Protocol «Cell removal from a living donor», the law may provide that the provisions of subparagraphs (i) and (ii) of paragraph 2 Art. 14 are not applied to cells to the extent stated above, if their removal involves only minimal risk and minimal risk for the donor [8].

Similar to the WHO GPs No. 5-8, provisions are in Art. 21 of the Convention «Prohibition of financial gain», as well as the same name art. 21 of Additional Protocol and Art. 22 «Prohibition of organ and tissue trafficking». The above prohibitions, in accordance with paragraph 1 of Art. 21 of Additional Protocol, do not prevent payments that do not form a financial advantage or are comparable to its benefits, in particular: compensation of living donors for loss of earnings and any other justifiable expenses caused by the removal or by the related medical examinations; payment of a justifiable fee for legitimate medical or related technical services rendered in connection with transplantation; compensation in case of unforeseen injury resulting from the removal of organs or tissues from living persons [5, 7, 8].

Similar to WHO GP No. 6, there are provisions in Article 19 «Promotion of donation» and Article 21 «Prohibition of financial gain» of Additional Protocol. According to paragraph 2 of Art. 21 of this protocol, advertising the need for or availability of organs or tissues, with a view to offering or seeking financial gain or comparable advantage, shall be prohibited [5, 8].

The recommended by WHO GPs No. 10 and 11 approaches were implemented into the legislation of the EU, USA, Canada, Australia and others. The world's leading countries have taken steps to create systems of safety and quality of cells, tissues and products based on them that are based on the risks associated with cell and tissue therapy products.

The EU has implemented three directives aimed at ensuring the quality and safety of human tissues and cells. They are Directive 2004/23/EC of 7 April 2004, 2006/17/EC of 8 February 2006 and 2006/86/EC of 24 October 2006 [12-14]. Directive 2004/23/EC sets standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. This directive applies to hematopoietic cells of peripheral blood, cord blood and bone marrow, reproductive cells, as well as embryonic tissues and stem cells of adults and embryos. The directive does not cover blood and blood products (except for hematopoietic progenitor cells), human organs and tissues of animal origin. Exception is also made of tissues and cells that are used as

autotransplants within a single surgical procedure that does not undergo any banking process [12].

To implement the basic Directive 2004/23/EC, two following «subsidiary» directives have been developed – Commission Directive 2006/17/EC as regards certain technical requirements for the donation, procurement and testing of human tissues and cells [13], and Commission Directive 2006/86/EC as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells [14]. The provisions of the latest Directive on tracking and reporting of serious adverse reactions and events are also applicable to the donation, supply and testing of human tissues and cells regulated by Directive 2006/17/EC. The above-mentioned EU directives [12-14] have taken into account the provisions of the Convention for the Protection of Human Rights and Dignity regarding the use of biology and medicine: Convention on Human Rights and Biomedicine (signed, but not ratified by Ukraine) [7], Additional Protocol to the Convention on Human Rights and Biomedicine on the Transplantation of Human organs and tissues [8], Guide to safety and quality assurance for organs, tissues and cells [49], are also reflected in GP and WHO recommendations [5].

In addition to the above guidelines, there are Regulation (EC) 1394/2007 On advanced therapy medicinal products and Commission Directive 2009/120/EC which amended the previously adopted Directive 2001/83/EC and Regulation (EC) 726/2004 for human cells and tissues used as advanced therapy medicinal products (ATMPs), which include gene therapy, somatic cell therapy or tissue engineering [15-18]. Cells and tissues for ATMPs undergo significant manipulations that change their biological characteristics, physiological functions or structural properties. In the recipient's body, they can perform other essential functions than those performed in the donor. In EU production and circulation of ATMPs is regulated by European Medicines Agency (EMA) as a production of medicines that requires compliance with Good Manufacturing Practice (GMP) and marketing authorization [15-18].

Together, the above directives create the minimum standards of quality and safety for the donation, obtaining, testing, processing, preservation, storage and distribution of human tissues and cells, as well as transparency of this activity while maintaining the confidentiality of the donor and the recipient. Activities related to cells and tissues for ATMPs undergo more strict regulation and control. With the participation of EMA, Guideline on Human Cell-based Medicinal Products [19] was developed which takes into account the provisions of the above-mentioned EU documents (Directive 2001/83/EC as amended, Regulation (EC) 1394/2007 for ATMP, Directives 2004/23/EC, 2006/17/EC and 2006/86/EC).

In the United States, legislative regulation of the production and distribution of Human Cells, Tissues, and Cellular And Tissue Based Products – HCT/Ps and bone marrow is based on a multilevel approach that takes into account potential risks from the application of technology or therapy based on certain cells, tissues or their products [20-25]. Products with high risk of adverse clinical outcomes require better control, more strict regulation and supervision. Products of cells and tissues for homologous use, removed with minimal manipulations, are considered low-risk products. Minimal manipulation means treatment that does not alter the relevant biological characteristics of cells, tissues or products based on them. Homologous use involves the elimination of damage, the reconstruction, replacement or additional introduction of cells, tissues or products based on them, which perform the same role and functions in the recipient as in the donor [21].

The bone marrow for homologous use, which has undergone minimal manipulation, i.e. for «normal» transplantation, falls under the jurisdiction of the Health Resources and Services Administration in accordance with section 379 of the Public Health Service Act – PHS Act) [22]. The National Organ Transplant Act (NOTA) [20] and section 371 of PHS Act define «bone marrow» as a «human organ» [23].

Unlike bone marrow, legal regulation of the production and distribution of human cells, tissues and products based on them is carried out by

the Food and Drug Administration (FDA) in accordance with sections 351 and 361 of the PHS Act [24, 25].

This is directly related to the FDA's Center for Biological Evaluation and Research (CBER), which regulates the use of human cells, tissues and products based on them for implantation, transplantation, infusion or transfer to the human body, including hematopoietic stem cells (HSCs). U.S. Department of Health and Human Services and CBER FDA published complex requirements Guidance for Industry Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) which includes requirements for premises, equipment, consumables, reagents, processing, process control, marking, storage, screening and testing of donors to prevent the transmission and spread of infectious diseases, as well as other processes [26].

Thus, the CBER FDA in accordance with Section 351 and/or 361 of PHS Act regulates HSCs of peripheral and umbilical cord blood transfusion, which have undergone minimal or greater than minimal manipulations, and donor lymphocytes (leukocytes) for infusion. Section 361 of PHS Act regulates the circulation of tissues and cells that do not require marketing authorization and meet the requirements of title 21 of the Code of Federal Regulations (CFR) of Part 1271, «Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement» («hereinafter 21 CFR 1271»). Criteria 21 CFR 1271.10 corresponds to HSCs of peripheral and cord blood, intended for autologous or allogeneic use in relatives of the first or second degree of affinity, undergone minimal manipulations, and intended for homologous use, which were not combined with other substances, except water, saline solutions, sterilizing or preserving agents in the process of production; and there is no safety problem. Such products must meet the requirements of the CGTP.

Other HSCs that do not meet the above criteria, subject to Section 351 PHS Act. Because of this approach, high-risk products are subjected to more stringent regulation as foreseen by section 351 PHS Act, and low-risk products – section 361 of this Law. The «351 products» are subjected to the same requirements as Medicines, Medical Products and/or Biological Products (Federal Food, Drug, and Cosmetic Act). They must demonstrate safety, efficacy and compliance with GTP and GMP requirements (21 CFR 210, 211 and 820), as well as, Investigational New Drug Requirements – IND (21 CFR 312) and Investigative Device Exemptions – IDE (21 CFR 812). Consequently, the normative requirements for HSCs from non-native donors for allogeneic transplantations are wider and more severe than for autologous and allogeneic related HSCT [21, 26, 27]. There is a similarity of regulatory approaches between the «351 products» in the US and the ATPMs in the EU.

In Canada, legislative system that distributes authority between the federal government and provincial/territorial governments regulate the production and circulation of cells, tissues and organs [28, 29]. According to the Food and Drugs Act [32], the federal government has the right to regulate the circulation of biological preparation, including the CTOs, in order to ensure their safety, efficiency and quality. Regulatory role is performed by the «Safety of Human Cells, Tissues and Organs for Transplantation Regulations» (CTORs) – CTOs Regulations [30] and the Medical Devices Regulations – MDRs [31]. These regulations establish minimum standards of quality and safety for the use of CTOs, as well as medical devices. Provinces and territories, on the other hand, are responsible for health and medical practices within their jurisdiction by regulating permission for donation and medical practice, as well as funding for organizations of provinces and territories responsible for receiving grafts [28-32].

The CTOs Regulations that came into force in 2007 apply to all persons and institutions involved in the collecting, processing, distribution or import of human CTOs for transplantation to another person which underwent minimal manipulations and are intended for homologous use [28-30]. If the cells or tissues have undergone more than minimal manipulations and/or are intended for non-homologous use, they are regu-

lated as medical products in accordance with MDRs [28, 29, 31]. CTOs Regulations outline the safety standards associated with screening, testing, assessing the suitability of donors; tests and measurements that are performed on CTOs after they are removed; preparation for their use in transplantation; preservation; quarantine; banking; packaging and marking; recording and reporting of errors, accidents and adverse reactions. CTOs Regulations prohibit the transplantation or import of any CTOs if they have been received or processed outside the facilities registered by Health Canada [30]. CTOs Regulations are based on National Standards of Canada, which include General Standard CAN/CSA Z900.1 for specific products – «Cells, Tissues, and Organs for Transplantation and Assisted Reproduction: General Requirements» [33].

Standard Z900.2.5 addresses issues related to the safety of human allogeneic and autologous lymphohematopoietic cells for homologous use that are used for human transplantation and includes requirements for the quality system (security aspects for potential and actual donors as well as recipients, staff and others persons who may receive transplantation or suffer from transplantation of these cells). In Canada, lymphohematopoietic cells for non-homologous use are subjected to Food and Drugs Act and relevant regulations. Standard Z900.2.5 applies to lymphohematopoietic cell transplantation facilities as well as institutions and individuals involved in lymphohematopoietic cell transplant-related activities: processing, including donor screening, testing and assessment of acceptability, and also obtaining of bone marrow, umbilical cord blood or cells for transfusion from the peripheral blood; cell safety assessment before transplantation; transplantation procedures; accounting; research and reporting on mistakes, accidents and adverse reactions; import/export; complaints and recalls.

Standard Z900.2.5 applies to institutions that (1) perform clinical transplant programs, provide conditions for (2) collecting and (3) processing of lymphohematopoietic cells. The listed institutions may be located in one place or be territorially separate and/or independent. Standard Z900.2.5 is intended to serve as a benchmark and provide the minimum requirements for monitoring safe practices in each of the listed activities. The standard does not apply to the collection, treatment or administration of erythrocytes, mature granulocytes, platelets, plasma, or plasma products intended for transfusion [34].

Therefore, for an effective transplantation, institutions are required to have a quality assurance system that meets the requirements of the above rules. Important components of the quality assurance system are standard operating procedures, which should be relevant and approved by a medical or scientific supervisor. A list of requirements for the treatment of specific CTOs, including lymphohematopoietic cells, is based on the above CAN/CSA Z900.1 standards, as well as the guidance for human CTOs transplant safety authorities published by Health Canada [35].

In Australia, the Therapeutic Goods Administration (TGA) carries out the regulation of activities with tissues, cells and products based on them for transplantation. TGA is a division of the Australian Government Department of Health, which is responsible for regulating medicines, medical products and biological products. TGA's responsibilities are not regulated by medical practice. Medical Board of Australia, with the support of the Australian Health Practitioner Regulation Agency (AHPRA), regulates medical practice through the development of standards, codes and guidelines for medical professions.

The work of TGA is based on the use of scientific and clinical experience in decision making to ensure that the benefits to consumers prevail over any risks associated with the use of drugs, biological products and medical products. In its activity, TGA is governed by the Therapeutic Goods Act 1989 (TG Act) [36], the Therapeutic Goods Regulations 1990 (TG Regulations) [37], the Therapeutic Goods Orders (TG Orders) that detail the technical requirements for specific products, including hematopoietic progenitor cells (HPCs) [38] and the Australian Code of Good Manufacturing Practice 2013 (GMP Code) for blood and tissues [39]. The above GMP code, along with relevant documents, covers human blood and its components, human tissues, products for cell therapy and HPCs [39, 40, 41].

To ensure the safety and quality of products, all therapeutic goods must be manufactured by manufacturers that meet the requirements of TG Act and TG Regulations, and in compliance with the principles of GMP Code [39, 40, 41]. In addition, the requirements may be specific to a particular product that is defined in detail in TG Orders. For example, in 2017, TG Order No. 94 (Standard for Haematopoietic Progenitor Cells derived from Cord Blood) was introduced for cord blood HPCs instead of the cancelled TG Order No. 75 [42]. According to it, cord blood-derived HPCs should comply with the Sixth Edition NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration, June 2016, published by NetCord and Foundation for the Accreditation of Cellular Therapy (NetCord-FACT International Standards) [53].

Australian manufacturers should have a production license issued by TGA. The license is issued when the compliance with the relevant production principles has been demonstrated. For HPCs, it is compliance with the existing GMP code [39, 40, 41]. An application for the inclusion of a therapeutic product in the Australian Register of Therapeutic Goods (ARTG) requires the submission of a dossier that includes detailed scientific and clinical information about the product. The degree of information required depends on the level of risk associated with the product. TGA evaluates the dossier for compliance with the standards and guidelines that exist in Australia. Only an approved TGA for use on Australian market and included in the ARTG product is eligible for use in Australia. In addition, TGA is committed to post-marketing regulation, supervision and monitoring. These measures may include inspection of production facilities, collection and evaluation of adverse event reports, and laboratory testing of product samples. TGA works with international regulators to detect signals that may indicate the security issues associated with the therapeutic product. In case of detecting the signal, TGA takes appropriate regulatory action. The requirements of the quality system are directed at the organizational structure, the system of monitoring and analysis by the management. They include many elements of the ISO 9000 Quality System standards.

By analogy with the regulatory framework for human tissues, cells and products based on them, adopted in America and Europe, transplants can be regulated in Australia as medicines, biological preparations or medical products, depending on their biological/mechanical properties or therapeutic uses. In Australia, based on product risk for the patient, four biological classes have been developed that take into account the degree of manipulation with the product and whether its application is homologous or not [43].

Class 1 is reserved for the least-regulated products. Manufacturers of Class 1 biologicals do not need a production license. Class 2 includes goods intended for homologous use, which have undergone minimal manipulations. They need assessment of the product manufacturing compliance and comply with other mandatory standards for inclusion in the ARTG. Class 1 and 2 products represent a low risk for the patient. Classes 3 and 4 include goods that have undergone more than minimal manipulations and/or are intended for non-homologous use. Class 3 includes goods that have undergone more than minimal manipulations, but their biochemical, physiological or immunological properties have not changed. Class 4 includes goods that have undergone more than minimal manipulations, in such a way that their biochemical, physiological or immunological properties have changed. Among these goods, the highest potential risk for the patient is class 4 goods. They require licensing documents similar to those of Class 2 goods, but with additional requirements for a comprehensive assessment of the dossier regarding product quality, safety and effectiveness and associated risks. The overall risk level for Class 4 goods is higher than for class 3 goods [43].

Australian legislation divides HPCs for the treatment of patients in three groups. HPCs used for a different purpose than the restoration of hematopoiesis are regulated as biologicals [43]. Fresh, viable HPCs (for example, bone marrow or umbilical cord blood) used to restore hematopoiesis are excluded from regulation as therapeutic preparations [43, 44]. HPCs used to restore hematopoiesis (in addition to the above, which are

excluded from regulation) are regulated as therapeutic goods, but not as biologicals. In accordance with current standards, bone marrow intended for transplantation from donor to recipient, as well as HPCs used for bone marrow regeneration produced in accordance with the GMP Code, are regulated as medicines and exempt from registration in the ARTG [43, 44, 45]. Because HPCs, collected, stored and supplied without a special change in their biological, mechanical and immunological properties, are used for «normal» transplantation. Today, in Australia, HSCT for bone marrow regenerating is a usual method of treating many diseases. Exclusion of HPCs for transplantation from the list of therapeutic goods does not apply to equipment and materials used for their manufacturing [45].

The above normative legal documents of the leading countries of the world regulate the general issues of manufacturing and circulation of tissues, cells and products based on them, including the bone marrow, peripheral and umbilical cord blood HSCs/HPCs transplantation. Today in the world, international special standards and guidelines directly related to HSCT have been developed. WHO, the EU and international and national professional communities, whose activities are related to HSCT, work on harmonizing and unifying these standards as well as terminology in the field of donation and transplantation.

WHO has issued two instructions concerning the basic requirements for the safety and efficacy of cells and tissues for transplantation [46, 47]. One of them, «Aide Mémoire on Key Safety Requirements for Essential Minimally Processed Human Essential Cells and Tissues for Transplantation» includes requirements for allografts of fresh bone marrow or peripheral blood derived from a living donor for transplantation, as well as cryopreserved cord blood cells [46].

The lack of generally accepted terminology and definitions in the field of cell, tissue and organ transplantation, as well as the need for a single understanding of the concepts for collecting data and information for a global database on donation and transplantation, prompted WHO to create «Global Glossary of Terms and Definitions on Donation and Transplantation» [48].

The CE published the «Guide to safety and quality assurance for organs, tissues and cells» and «Guide to the quality and safety of tissues and cells for human application», which contain requirements for donors and ensure the quality and effectiveness of bone marrow, peripheral and cord blood HSCs [49, 50]. These documents contain provisions that are considered «minimum standards» that are in line with the principles set out in the relevant EU directives. These guides provide technical support to both EU Member States that have implemented or are implementing directives and those non-EU countries, but are considering their adoption in order to unify the standards for ensuring the quality and safety of tissues and cells for transplantation, including HSCs from all sources.

Among international professional organizations, American Society for Blood and Marrow Transplantation – ASBMT, American Association of Blood Banks – AABB, Foundation for the Accreditation of Cellular Therapy – FACT (FACT-Netcord), International Society for Cellular Therapy – ISCT (ISCT-Europe), European Group for Blood and Marrow Transplantation – EBMT, World Marrow Donor Association – WMDA, European Federation for Immunogenetics – EFI played a leading role in the development and unification of standards. The aforementioned organizations have created the Alliance for Harmonization of Cellular Therapy Accreditation (AHCTA), which represents Joint Accreditation Committee ISCT-EBMT – JACIE. AHCTA released Global Standard for Donation, Collection, Testing, Processing, Storage, and Distribution of Allogeneic HSCs and Related Cellular Therapies [51].

International professional organizations have proposed a minimum set of standards for harmonization of the activities associated with HSCT – FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration, which are applied to HSCs irrespective of their origin (bone marrow, peripheral and umbilical/placental blood). These standards are applied to all phases of harvesting, processing, storage and administration of cells derived from bone marrow or peripheral blood, including various manipulations such as removal

or enrichment of various cell populations, expansion of hematopoietic cell populations, and cryopreservation. Accreditation of clinical applications has been developed for allogeneic transplantation, autologous transplantation, or both. Transplantation of umbilical/placental blood is included in the standards of allogeneic or autologous transplantation. There are programs for accreditation for HSCT in adult and pediatric patients [52].

For the accreditation of institutions engaged in collection and/or banking of umbilical cord blood, NetCord-FACT developed Sixth Edition NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration. These standards do not cover clinical transplantation of umbilical/placental blood cells [53].

WMDA developed International Standards for Unrelated Hematopoietic Progenitor Cell Donor Registries and Guidelines for collection and transportation of haematopoietic progenitor cells (HPCs-BM, apheresis and the therapeutic cells – T Cells)

Another international non-profit non-governmental organization is International Council for Commonality in Blood Bank Automation – IC-CBBA that is responsible for development and management of Information Standard for Blood and Transplant – ISBT 128. ISBT 128 is an international standard in terms of terminology, identification, coding, marking of medicinal products of human origin, including HSCs. It is used in more than 77 countries. The standard was developed to ensure a high level of accuracy, safety and efficacy of transplants, as well as tracking the origin of CTOs for transplantation [56, 57, 58].

Thus, the above-mentioned international professional organizations have undertaken work to harmonize and unify relevant standards and guidelines at the global level in order to create a single set of professional requirements for the quality and safety of cell therapy, including the use of HSCs derived from bone marrow, peripheral and umbilical cord blood. As a rule, their requirements for HSCs, which have undergone minimal manipulations and are intended for homologous application, are in accordance with the relevant legal acts of the EU, the USA, Canada and Australia. This is important for the international transplant exchange, since more than 40 % of HSCT in the world is due to the involvement of donors from abroad [51]. The above regulatory documents are summarized in **Table 1**.

ANALYSIS OF REGULATORY FRAMEWORK OF UKRAINE IN THE FIELD OF TISSUE AND CELL TRANSPLANTATION

To date, Ukraine has a limited number of legislative and regulatory acts that directly regulate the activities related to HSCT. Activities related to the transplantation of organs, tissues and cells are regulated by the Laws of Ukraine on transplantation that consist of the Fundamentals of the Ukrainian Legislation on Health Care of November 19, 1992, No. 2801 XII (hereinafter, «Fundamentals of Legislation on Health Care») [59], Law of Ukraine «On transplantation of organs and other anatomical materials to a human» of July 16, 1999, No. 1007-XIV (hereinafter, the Law of Ukraine «On transplantation»); as well as other normative legal acts of Ukraine adopted in accordance with them [60].

In the Law of Ukraine «On Transplantation» there are no such definitions as «hematopoietic stem cells» or «hematopoietic progenitor cells», as well as sources of their origin. According to the terminology of the Law of Ukraine «On Transplantation» (Article 1), the bone marrow, peripheral and umbilical cord blood HSCs fall under the definition of «anatomical materials» (organs, tissues, anatomical formations, human or animal cells) and «homotransplants» (human anatomical materials, intended for transplantation). An important property of these homotransplants is their ability to regeneration.

The application of the transplantation of anatomical materials from the donor to the recipient is carried out according to the law in case of their consent or consent of their legal representatives, provided that the use of other means and methods for life support, restoring or improving the health does not have the desired results, but caused harm to the donor is less than that which threatened the recipient. Taking into account the current state of science and recommendations of the WHO, The Law of Ukraine «On Transplantation» defines the conditions and procedure for

transplantation as a special treatment method; ensures observance of human rights in Ukraine and protection of human dignity in transplantation and implementation of other activities related to it.

Art. 1 of the Law of Ukraine «On Transplantation» defines transplantation as a special method of treatment, which consists in transplanting the recipient of an organ or other anatomical material taken from a person or an animal [60]. According to Art. 3 the scope of the Law of Ukraine «On Transplantation» applies to activities related to the donation, storage, transportation of organs, other anatomical materials of a human and their transplantation, manufacture of bioimplants, obtaining and application of xenografts. The action of this Law does not apply to: blood donation and/or its components and activities related to their use; autotransplantation – transplantation to a person of his/her anatomical material; activity of banks of umbilical cord blood, other tissues and cells of a person according to the list approved by the central executive body, which ensures the formation of state policy in the field of health care.

The activity of banks of umbilical cord blood, other tissues and human cells according to the list approved by the Ministry of Health of Ukraine is subjected to licensing in accordance with the Law of Ukraine «On Licensing Types of Economic Activity» [61]. Licensing conditions for conducting business of these banks was approved by the Resolution of the Cabinet of Ministers of Ukraine dated March 2, 2016 #286 «On Approval of Licensing Conditions for the Operation of the Activity of the Cord Blood, Other Human tissues and cells bank in accordance with the list approved by the Ministry of Health» [62].

Thus, the effect of the Law of Ukraine «On Transplantation» extends only to allogeneic transplantation of anatomical materials from related and non-related donors. According to Art. 290 «Right to Donate» of the Civil Code of Ukraine, an adult capable active natural person has the right to be a donor of blood, its components, as well as organs and other anatomical materials and reproductive cells. The person of the donor should not be familiar to the recipient, and recipient's person to donor's family, except when the recipient and the donor are married or close relatives [63].

As donors of peripheral blood and/or bone marrows HSCs, only living related or non-related donors are used. According to Art. 12 of the Law of Ukraine «On Transplantation», a living donor can be only an adult capable person. Removing of a homotransplant from a living donor is allowed on the basis of a conclusion of the physician's consultation of the appropriate health care institution or research institution after its comprehensive medical evaluation and provided that the harm done to the donor's health will be less than the harmful health risk that threatens the recipient. In order to capture transplants that are capable of regeneration, the recipient and the donor need not be married or be close relatives. It is not allowed to remove homograft from living persons held in places of detention; suffer from severe mental disorders; have a disease that can be transmitted to the recipient or harm his health; previously provided organ or a part of the organ for transplantation [60].

Thus, Ukrainian legislation strictly (without exception for cells and tissues capable of regeneration) prohibits donation for minors and incapacitated persons. Although, existing international legal instruments allow such exceptions for family donation of regenerating cells, when there is no appropriate adult donor. These exceptions are given in the commentary to WHO GP No. 4, paragraph 2 of Art. 20 of the Convention and Art. 14 and 15 of Additional Protocol [5, 7, 8]. It is noted that in any case, the objection of a minor to conduct the procedure of donation should prevail over the consent provided by any other party. The opinion of a minor is counted as a determining factor, the importance of which increases in proportion to the age and maturity of this person. The provisions applicable to minors also apply to any incapacitated person [5, 7, 8].

According to Art. 13 of the Law of Ukraine «On Transplantation», a homotransplant may be obtained from a living donor, only if there is a written consent about it, signed intentionally and without coercion, after a doctor has given him/her objective information about possible complications for his/her health, as well as about his/her rights connected to the performance of the donor function. In the application form, the donor

 Table 1. International and national acts in the field of tissues and cells transplantation, including HSCT.

NO.	TITLE OF THE DOCUMENT	YEAR OF PUBLICATION	REFERENCE
1.	WORLD HEALTH ORGANIZATION		
1.1	Resolution WHA63.22 on human organ and tissue transplantation.	2010	[5]
1.2	Aide Mémoire on Key Safety Requirements for Essential Minimally Processed Human Essential Cells and Tissues for Transplantation	2004	[46]
1.3	Aide-Mémoire on Access to Safe and Effective Cells and Tissues for transplantation	2006	[47]
1.4	Global Glossary of Terms and Definitions on Donation and Transplantation	2009	[48]
2.	EUROPEAN UNION		
2.1	Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine	2005	[7]
2.2	The Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Transplantation of Organs and Tissues of Human Origin	2002	[8]
2.3	Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells	2004	[12]
2.4	Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells	2006	[13]
2.5	Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells	2006	[14]
2.6	Commission Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use	2001	[16]
2.7	Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency	2004	[17]
2.8	Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004	2007	[15]
2.9	Commission Directive 2009/120/EC of 14 September 2014 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products	2009	[18]
2.10	Guideline on Human Cell-based Medicinal Products (EMA/CHMP/410869/2006)	2008	[19]
2.11	Guide to safety and quality assurance for organs, tissues and cells, 2 nd edition	2004	[49]
2.12	Guide to the quality and safety of tissues and cells for human application. 3 rd Edition	2017	[50]
3.	INTERNATIONAL PROFESSIONAL ORGANIZATIONS		
3.1	Towards a Global Standard for Donation, Collection, Testing, Processing, Storage, and Distribution of Allogeneic HSC and Related Cellular Therapies	2008	[51]
3.2	Circular of Information for the use of cellular therapy products	2009	[2]
3.3	FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration, Sixth Edition – Version 6.1	2015	[52]
3.4	Sixth Edition NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration	2016	[53]
3.5	World Marrow Donor Association International Standards for Unrelated Hematopoietic Progenitor Cell Donor Registries	2014	[54]
3.6	World Marrow Donor Association (WMDA) Guidelines for couriers and the transportation of haemopoietic progenitor cells (HPC-BM, apheresis and therapeutic cells-T Cells), Version 5.4	2009	[55]
3.7	Introduction and Importance of a Globally Unique Identity and Labelling Format (ISBT 128)	2011	[56]
3.8	ISBT 128 Standard. Standard Terminology for Medical Products of Human Origin For Use with Product Description Code Database. Version 7.10	2010	[57]



NO.	TITLE OF THE DOCUMENT	YEAR OF PUBLICATION	REFERENCE
4.	USA		
4.1	National Organ Transplant Act / Public Law 98-507	1984	[20]
4.2	21 CFR Parts 16, 1270, 1271: Current good tissue practice for human cell, tissue, and cellular and tissue-based product establishments; Inspection and Enforcement; Final rule	2004	[21]
4.3	Public Health Service Act. Part I – C.W. Bill Young Cell Transplantation Program. Section 379	2011	[22]
4.4	Public Health Service Act. Part H – Organ Transplants. Organ procurement organizations. Section 371	2011	[23]
4.5	Public Health Service Act. Part F – Licensing – Biological Products and Clinical Laboratories. Subpart 1 – Biological Products. Regulation of biological products. Section 351	2011	[24]
4.6	Public Health Service Act. Part G – Quarantine and Inspection. Control communicable disease. Section 361	2011	[25]
4.7	Guidance for Industry Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/PS)	2011	[26]
5.	CANADA		
5.1	Background Paper for the OTDT Committees: Organ and Tissue Donation and Transplantation Legislative and Legal Framework	2011	[28]
5.2	Background Paper for the Tissue Expert Committee: How can the Canadian tissue donation and transplantation system best ensure consistent safety and quality?	2011	[29]
5.3	Safety of Human Cells, Tissues and Organs for Transplantation Regulations. SOR/2007-118	2017	[30]
5.4	Medical Devices Regulations. SOR/98-282	2017	[31]
5.5	Food and Drugs Act. R.S.C., 1985, c. F-27	2017	[32]
5.6	CAN/CSA-Z900.1-17 – Cells, tissues, and organs for transplantation: General requirements	2017	[33]
5.7	CAN/CSA-Z900.2.5-17 – Lymphohematopoietic cells for transplantation	2017	[34]
5.8	Guidance Document for Cell, Tissue and Organ Establishments: Safety of Human Cells, Tissues and Organs for Transplantation	2017	[35]
6	AUSTRALIA		
6.1	Therapeutic Goods Act 1989	2014	[36]
6.2	Therapeutic Goods Regulations 1990	2017	[37]
6.3	Therapeutic Goods Order No. 88 – Standards for donor selection, testing and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products	2013	[38]
6.4	Therapeutic Goods Order No. 94 (Standard for Haematopoietic Progenitor Cells derived from Cord Blood) 2017	2017	[42]
6.5	Australian Code of Good Manufacturing Practice for human blood and blood components, human tissues and human cellular therapy products. Version 1.0	2013	[39]
6.6	Therapeutic Goods (Manufacturing Principles) Determination No.1 of 2013	2017	[40]
6.7	Guideline for the Preparation of Technical Master Files for Blood, Blood Components and Haematopoietic Progenitor Cells. Third edition, 2008	2008	[41]
6.8	Australian Regulatory Guidelines for Biologicals. Part 1 – Introduction. Part 1 – Introduction to the Australian Regulatory Guidelines for Biologicals. Version 2.0, June 2017	2017	[43]
6.9	Therapeutic Goods (Things that are not Biologicals) Determination No. 1 of 2011	2011	[44]
6.10	Excluded Goods Order No.1 of 2011.Guideline for Items 4(o), 4(p), 4(q) and 4(r).Version 1.1, March 2013	2013	[45]

must indicate his consent to the taking of a transplant and his awareness of the possible consequences. The signature of the donor on the application is certified in accordance with the procedure established by law, and the application is attached to his/her medical documentation [60].

Features of donation and transplantation of bone marrow and other capable of regeneration anatomical materials are defined in Art. 14 of the Law

of Ukraine «On Transplantation». According to it, removing of bone marrow and other capable of regenerating anatomical materials from a living donor is carried out in compliance with the requirements of the above articles 12 and 13 of this law. With the consent of the donor and in the absence of medical contraindications for it, bone marrow, and others capable of regeneration, anatomical materials can be repeatedly collected. At the request

of an adult capable person, at his/her expense, bone marrow can be stored to use in case of need for autotransplantation. With the consent of the donor, his/her bone marrow can be provided free of charge or for payment for transplantation to another person. For workers employed at work with an increased risk of damage to the hematopoietic system, bone marrow collection is carried out at the expense of the employer. The procedure for collection, storing and application of bone marrow is established by the Cabinet of Ministers of Ukraine [60].

Art. 18 of the Law of Ukraine «On Transplantation» prohibits trade of human organs and other anatomical materials. In Ukraine, the agreements on the sale of human organs or other anatomical materials, with the exception of bone marrow, is prohibited [60]. Ability to buy and sell bone marrow, which is allowed by Ukrainian legislation in Art. 14 and 18, contradicts WHO GP No. 5, Art. 21 of the Convention and Art. 21 and 22 of Additional Protocol prohibiting the purchase or offer of the purchase of cells, tissues or organs for transplantation or their sale by a living donor or the immediate relatives of the deceased. However, the prohibition on the sale or purchase of cells, tissues or organs does not exclude the reimbursement of reasonable and controlled expenses incurred by a donor, including loss of income, or payment of expenses related to the care, processing, preservation and transfer of human cells, tissues or organs for transplantation. This approach allows to compensate for donor-related costs (including medical expenses and loss of income by living donors) so that these factors do not create an obstacle for donors to implement their intentions [5, 7, 8].

The rights of the person who has agreed to become a donor and a living donor are given in Art. 22 of the Law of Ukraine «On Transplantation». According to this article, a person who has agreed to become a donor, before obtaining a homotransplant, has the right to withdraw their previous consent. In case of donor's death, infection, the emergence of other illnesses or health hazard related to donation, he/she is subject to compulsory state insurance. The donor, in accordance with the procedure established by the law of Ukraine, shall be compensated for the health hazard related to donation, taking into account additional expenses for treatment, enhanced nutrition and other measures aimed at social, work and professional rehabilitation [60]. In fact, the provisions of this article are not fulfilled. Currently there is no procedure for compulsory state insurance of donors, as well as the procedure for reimbursement of harm caused to the donor's health by donation.

According to Art. 22, a person, who has agreed to become a donor, before donation HSCs of peripheral blood or bone marrow has the right to withdraw their previous consent. This rule does not take into account HSCT specifics. After all, if the donor withdraws to provide a donation during or after the recipient's myeloablative conditioning regime, it can lead to the death of the patient. Thus, in the voluntary consent of the HSCs donor, there should also be provisions that allow the withdrawal of the consent until the medical intervention to the recipient does not reach the stage at which the recipient is in danger in case of termination of HSCT [5].

Art. 23 of the Law of Ukraine «On Transplantation» provides social protection of the donor and members of his family. Disability of the donor, caused by performance of the donor function, is equal to invalidity due to job-related injury or occupational disease. In the event of donor's death resulting from the performing of the donor function, the members of the family of the deceased, who were in his maintenance, are granted survivor's pension. The appointment of such a pension is carried out in accordance with the procedure and conditions established by the legislation of Ukraine to grant a pension to the breadwinner family who died because of job-related injury or occupational disease [60].

Art. 17 The Law of Ukraine «On Transplantation» defines the procedure for the use of organs of deceased donors for transplantation, as well as interstate exchange of homotransplants. According to this article, Ukraine has a Unified state information system of transplantation (USIST), which provides information on recipients, as well as individuals who have declared their consent or disagreement to become donors in case of death. This information is confidential; it is a medical secrecy and

can only be disclosed in cases provided by this law. The central executive body, which ensures the formation of the state policy in the field of healthcare, approves the Regulation on USIST and ensures the activity of such a system.

In accordance with Art.17, if there is not a recipient biologically compatible with the received organ within Ukraine, the central executive authority, which ensures the formation of health care policy, provides information on these bodies to relevant institutions and organizations of other countries, with which Ukraine has concluded international agreements on transplantation issues. Organs removed from deceased persons, as well as bone marrow removed from living donors, may be transferred to other countries only on an equal exchange basis in accordance with the procedure established by the relevant international treaties of Ukraine [60]. In fact, provided by Art. 17 of the Law of Ukraine «On Transplantation», at the beginning of 2018 USIST has not been established and does not function.

The second group of normative acts consists of resolutions of the Cabinet of Ministers of Ukraine and orders of the Ministry of Health of Ukraine, regulations, instructions, etc. We will consider the most important sub-legal acts that regulate the activities associated with HSCT. Among them, a special position is taken by the Resolution of the Cabinet of Ministers of Ukraine of April 24, 2000 No. 695 «Some issues of the implementation of the Law of Ukraine «On organ transplantation and other anatomical materials to a human» [64]. After all, according to Art. 8 of the Law of Ukraine «On Transplantation» activities related to transplantation may be carried out by state and municipal health care institutions and state research institutions accredited in accordance with the legislation of Ukraine, in accordance with the list approved by the Cabinet of Ministers of Ukraine. The above-mentioned resolution approved a list of state and municipal health care institutions and state research institutions that have the right to carry out activities related to transplantation of human organs and other anatomical materials in Ukraine. The above list contains seven sections that share institutions of health care and research institutions entitled to carry out: activities related to transplantation of organs and other anatomical materials; activities related to human organs transplantation; activities related to human tissue transplantation; activity related to human cell transplantation; activity related to transplantation of tissues and cells to humans with burn injuries; removal of organs from deceased donors; to carry out obtaining of anatomical materials from deceased donors for further tissue transplantation and bioimplant preparation [64]. The article «Health facilities and scientific institutions that have the right to carry out activities related to human cell transplantation» contains health care facilities and research institutions that have the right to perform HSCT [64].

Another normative legal act directly related to HSCT is the Order of the Ministry of Health of Ukraine «On approval of regulatory acts on organ transplantation and other anatomical materials to a person» of May 4, 2000, No. 96 [65]. This order approved the Procedure for the collecting, storage and application of bone marrow [66].

To prevent the transmission of infectious diseases from a donor to a recipient, the Order of the Ministry of Health of Ukraine of June 10, 2004, No. 294 approved the «List of measures to prevent the transmission of infectious diseases at organs transplantation and other anatomical materials to a person» [67].

At present in Ukraine, the use of umbilical cord blood as a source of HSCs for transplantation is possible only in the form of clinical trials. The procedure for carrying out clinical trials of tissue and cell transplants and evaluation of materials of clinical trials, including transplantation of the cord blood HSCs, was approved by the Order of the Ministry of Health of Ukraine of October 10, 2007, No. 630 «On Approval of the Procedure for Conducting Clinical Trials of Tissue and Cell Transplants and the Evaluation of Materials for Clinical Trials and Changes to the Procedure for carrying out clinical trials of medicinal products and evaluation of materials of clinical trials, approved by the order of the Ministry of Health of Ukraine of February 13, 2006 No. 66, registered in the Ministry of Justice of Ukraine on March 10, 2006 under No. 252/12126» [68].

To improve the provision of medical care to paediatric patients, the Order of the Ministry of Health of Ukraine «On Approving the Clinical Protocol Allogeneic and autologous transplantation of stem hematopoietic cells in children. Indications and contraindications» of July 23, 2010, No. 619 approved the above-mentioned protocol, which is based on EBMT scientific data on clinical practice in the field of HSCT in Europe [69].

In order to organize the search for non-related donors for allogeneic HSCT, according to Art. 17 of the Law of Ukraine «On Transplantation» [60] and guided by the Regulation on USIST [73], the Order of the Ministry of Health of Ukraine of September 28, 2009, No. 247-o «On Amendments to the Statute of the State Enterprise «State Pharmacological Center» Ministry of Health of Ukraine», All-Ukrainian register of donors of hematopoietic stem cells (bone marrow) of the Ministry of Health of Ukraine» (hereinafter «Ukrainian Register of Donors of HSCs»), which is the basic research centre for the search of all potential donors of HSCs (bone marrow) in Ukraine, which cooperates with transplantation centres and coordinates the activity of the centres of bone marrow HSCs collecting and HLA-laboratories. According to this order, it is entrusted with the following functions: creation and information filling of the data bank of «All-Ukrainian HSCs Donors Register»; receiving of requests for the search of compatible non-related donors of bone marrow from transplantation centres and/or search centres; search of compatible donors in the database of «Ukrainian HSCs Donors Register» and their activation; coordination of donor HSCs collection in the centre; organization of transportation of HSCs to the transplantation centre; coordination of work related to the performing of allogeneic bone marrow transplantation. However, international exchange of HSCs transplants will be possible only if Ukrainian HSCs Donors Register implements international standards and requirements of the WMDA and BMDW and joins these organizations.

A special place in the system of provision of transplant care is given to the Coordination Centre for the Transplantation of organs, tissues and cells of the Ministry of Health of Ukraine (hereinafter Coordination Centre) and its subordinate USIST. Coordination centre, in accordance with the Resolution of the Cabinet of Ministers of Ukraine of April 27, 1994, No. 257 «On the Establishment of the Coordination Centre for the Transplantation of Organs, Tissues and Cells», is entrusted to provide organization, advisory and methodological work in the field of organ, tissue and cell transplantation [70]. According to the Order of the Ministry of Health of Ukraine «On approval of the Regulation on the Coordination Centre for Transplantation of Organs, Tissues and Cells» of December 11, 2006. No. 812 the main tasks of the Centre are:

- organizational and methodical guidance, information provision, control, provision of cooperation between institutions and organizations carrying out activities related to transplantation;
- realization of scientific researches and introduction of scientific developments in the field of transplantation of organs, tissues and cells in practical medicine;
- maintenance of USIST [71].

Moreover, the Resolution of the Cabinet of Ministers of Ukraine of September 5, 2007 No. 1100 «On Measures to Organize the Activities of Health Care Institutions and Scientific Institutions Related to the Transplantation of Organs, Tissues and Cells» established that the Coordination Centre:

- is the main scientific and practical institution that organizes and conducts clinical trials of tissue and cell transplants at the expense of voluntary contributions from legal entities and individuals and other sources not prohibited by law;
- controls the activities of healthcare and scientific institutions, regardless of their subordination, related to the transplantation of organs, tissues and cells [72].

For effective and operational information support of the transplantation system in Ukraine, to provide informational cooperation with relevant institutions of other countries and specialized international organizations, form specialized information resources and provide information services, the framework of the Coordination Centre provide the USIST, which has not been created to date.

According to the Order of the Ministry of Health of Ukraine of November 29, 2002 No. 422, «On Approval of the Regulation on Unified State Information System of Transplantation» [73], the main tasks of this system are to ensure:

- information support of measures on the development and implementation of state policy in the field of transplantation;
- improvement of collection, archiving, prompt processing and transfer of information about recipients and donors, consent or disagreement to become donors in case of death, anatomical materials, bioimplants and their use for transplants and implants, etc.;
- confidentiality of information about recipients, as well as about persons who have declared their consent or disagreement to become donors in case of death;
- prompt search for recipients in Ukraine and informing the relevant institutions and organizations of other countries with which Ukraine has signed international transplant treaties;
- monitoring the health status of recipients in the postoperative period;
- introduction of standardized and certified information and analytical support for all part of the transplantation system;
- unified standards and information technologies for electronic documentation in institutions of transplantation system;
- information support for the development and implementation of state and international transplantation programs;
- implementation of control and analytical procedures to ensure the functioning of the transplantation system;
- prompt information to the Ministry of Health of Ukraine on activities related to transplantation;
- activity of the system of target training and certification of personnel for the system of transplantation, including distance learning methods.

To carry out the above tasks, USIST should include:

- databases and registers of organs, anatomical materials, bioimplants; donors and recipients; agreements and withdraws for donations; performed transplantations; forms and activities related to transplantation; state and municipal health care institutions, state research institutions, which are allowed to carry out activities related to transplantation, regulatory framework and information resources;
- functional subsystems for typing organs and other anatomical materials, selection of recipients in Ukraine, providing information to relevant institutions and organizations of other countries, verification, archiving, administration, accreditation, certification, logistics, telecommunications and communications;
- information systems (databases, registers, functional subsystems) of state and municipal health care institutions, state research institutions, which are allowed to carry out activities related to transplantation [73].

The analysis of the above-mentioned and other [74-76] legal acts suggests that they regulate mainly activities related to organ transplantation, and do not take into account the features and specificities of HSCT.

In our country on 16.09.2014 there was adopted the Law of Ukraine «On ratification of the Association Agreement between Ukraine, on the one hand, and the European Union, the European Atomic Energy Community and their Member States, on the other hand» (hereinafter «Association Agreement» «[77]. In accordance with Art. 427 and 428 «Association Agreement», cooperation between Ukraine and the EU covers such areas as the quality and safety of substances of human origin, including blood, tissues and cells. Ukraine should gradually bring its legislation and practice closer to the principles of the EU *acquis*, in particular in the field of infectious diseases, blood services, tissue and cell transplantation [78]. The list of relevant EU *acquis* acts is set out in Annex XLI of this Agreement [79].

By ratifying the «Association Agreement», Ukraine has confirmed its intentions regarding the gradual approximation of its legislation to EU

Table 2. Legislative acts of Ukraine in the field of tissues and cells transplantation, including HSCT.

NO.	TITLE OF THE DOCUMENT	REFERENCE
1.	Fundamentals of Ukrainian Health Care Legislation No. 2801 XII of November 19, 1992	[59]
2.	Law of Ukraine "On transplantation of organs and other anatomical materials to a person" of July 16, 1999 No. 1007-XIV	[60]
3.	Civil Code of Ukraine of January 16, 2003 No. 435-IV	[63]
4.	Law of Ukraine "On Licensing of Types of Economic Activities" of March 2, 2015, No. 222-VIII	[61]
5.	Law of Ukraine "On ratification of the Association Agreement between Ukraine, on the one hand, and the European Union, the European Atomic Energy Community and their Member States, on the other hand" of September 16, 2014, No. 1678-VII	[77]
6.	The Association Agreement between Ukraine, on the one hand, and the European Union, the European Atomic Energy Community and their Member States, on the other hand, of November 30, 2015. Annex XLI to Chapter 22 "Public Health", Section V "Economic and Industrial Cooperation».	[78, 79]
7.	Resolution of the Cabinet of Ministers of Ukraine of April 27, 1994 No. 257 "On the Establishment of the Coordination Centre for the Transplantation of Organs, Tissues and Cells"	[70]
8.	Resolution of the Cabinet of Ministers of Ukraine of April 24, 2000 No. 695 "Some issues of the implementation of the Law of Ukraine" On the Transplantation of Organs and Other Anatomical Materials to a Person "	[64]
9.	Resolution of the Cabinet of Ministers of Ukraine of September 5, 2007 No. 1100 "On Measures for the Organization of the Activities of Health Care Institutions and Research Institutions Related to the Transplantation of Organs, Tissues and Cells"	[72]
10.	Resolution of the Cabinet of Ministers of Ukraine of March 2, 2016, No. 286 On Approval of Licensing Conditions for the Economic Activity of the Bank of Cord Blood, Other Human Tissues and Cells in accordance with the list approved by the Ministry of Health	[62]
11.	Order of the Ministry of Health of Ukraine "On approval of regulatory acts on organ transplantation and other anatomical materials to a person" of May 4, 2000 No. 96	[65]
12.	The order of collecting, storing and use of bone marrow	[66]
13.	Order of the Ministry of Health of Ukraine "On the List of Measures to Prevent the Transmission of Infectious Diseases at the Transplantation of Organs and Other Anatomical Materials to a Person" of June 10, 2004, No. 294	[67]
14.	Order of the Ministry of Health of Ukraine of January 10, 2007 No. 630 "On Approval of the Procedure for Conducting Clinical Trials of Tissue and Cell Transplants and the Evaluation of Materials of Clinical Trials and Changes to the Procedure for Conducting Clinical Trials of Medicinal Products and Evaluation of Materials of Clinical Trials approved by the Order of the Ministry of Health of Ukraine of February 13, 2006 No. 66 , registered in the Ministry of Justice of Ukraine of March 10, 2006 No. 252/12126 "	[68]
15.	Order of the Ministry of Health of Ukraine "On Amendments to the Statute of the State Enterprise" State Pharmacological Centre "of the Ministry of Health of Ukraine of September 28, 2009 No. 247-o	-
16.	Order of the Ministry of Health of Ukraine "On Approval of Clinical Protocol" Allogeneic and autologous transplantation of stem-cell hematopoietic cells in children. Indications and contraindications "of July 23, 2010, No. 619	[69]
17.	Order of the Ministry of Health of Ukraine "On Approval of the Regulation on the Coordination Centre for the Transplantation of organs, tissues and cells" of December 11, 2006 No. 812	[71]
18.	Order of the Ministry of Health of Ukraine "On Approval of the Regulation on the Uniform State Information System of Transplantation" of November 29, 2002 No. 422	[73]
19.	Order of the Ministry of Health of Ukraine "On the Regulation of the Transplantation Service of Ukraine" of May 24, 2004 No. 261	[74]
20.	Order of the Ministry of Health of Ukraine "On Medical Centers (Branches) of Transplantation of Organs and Other Anatomical Materials" of July 26, 2004 No. 374	[75]
21.	Order of the Ministry of Health of Ukraine "On approval of regulatory documents on transplantation issues" dated September 25, 2000 No. 226	[76]

legislation. Within two years from the date of entry into force of «Association Agreement», a number of EU directives on tissue and cell transplantation should be implemented in Ukraine, that is: Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells [12]; Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells [13]; Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/

EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells [14].

The action of the above directives applies to autologous and allogeneic HSCs of bone marrow, peripheral blood and umbilical cord blood [12-14]. The introduction of the provisions of these directives in the normative and legal documents of Ukraine in the field of tissue and cell transplantation will allow to unify the requirements for ensuring quality and safety for HSCs of bone marrow, peripheral and umbilical cord blood with the relevant EU standards. The above normative legal documents

of Ukraine regulating the transplantation of tissues and cells, including HSCT, are summarized in **Table 2**.

Thus, the analysis of the Laws of Ukraine suggests that the Law of Ukraine «On Transplantation» and other normative legal acts regulate mainly activities related to organ transplantation, and the features of the HSCT are not taken into account. Today, a number of terms are used, which are not provided in legal acts, which may cause a variety of legal conflicts. The Law of Ukraine «On Transplantation» contains terms such as «autotransplantation» and «bone marrow transplantation», but such commonly accepted concepts as «allogeneic transplantation» and «transplantation of hematopoietic stem (progenitor) cells» are not used. In the Law of Ukraine «On Transplantation» there are no such definitions as «hematopoietic stem cells» or «hematopoietic progenitor cells», as well as sources of their origin (bone marrow, peripheral blood and umbilical cord blood) are not fixed.

The Law of Ukraine «On transplantation» applies only to allogeneic transplantation. The main type HSCT – an autologous transplantation, remains out of the attention of the Law, which is not subjected to its action. Fixation of attention on the second according to the value source of HSCs – bone marrow, leaves out the attention of the main and most used source of HSCs – peripheral blood. At the present stage in Ukraine, the application of the third valuable source of HSCs – umbilical cord blood, is possible only in the form of clinical trials. The Law of Ukraine «On Transplantation» does not apply to the activities of umbilical cord blood banks – healthcare institutions that carry out activities related to the umbilical cord blood transportation, processing, cryopreservation and storage.

Nowadays in Ukraine, according to the Law of Ukraine «On Transplantation», the procedure for state insurance of living donors for homotransplants in case of death of a donor, infection, emergence of other diseases or health hazard related to donation, as well as the procedure for compensation of harmful health risk, including additional expenses for treatment, enhanced nutrition and other measures aimed at social, work and professional rehabilitation.

Provided by the Law of Ukraine «On Transplantation», USIST has not been established. Exchange of HSCs transplants with international structures outside USIST is not possible. The effective work of the Ukrainian register of donors of hematopoietic stem cells (bone marrow) of the Ministry of Health of Ukraine as a subsystem of USIST, responsible for filling registries by typed donors of HSCs, as well as the search for histocompatible donors of HSCs and transplant exchange within Ukraine and abroad, have not been established. The work of the above registry should be built in accordance with the standards and requirements of the WMDA, BMDW and the EU Directives on the quality and safety of human tissues and cells.

There should be revised a provision of the Law of Ukraine «On Transplantation» regarding the possibility of bone marrow purchase and selling as contrary to international standards in the field of transplantation. It is more advisable to talk about compensation to donors of HSCs for their donor functions. In addition, there are no clear criteria for the accreditation of the centres and branches of HSCT, unified approaches to the type of donor and recipients, as well as standards for the provision of trans-

plant assistance at various diseases. There is a need to develop integrated mechanisms to ensure the quality of transplantation care and control of its use. The development of quality and safety standards for HSCs transplants is necessary. At present, there is no procedure for importing to and exporting of HSCs transplants from Ukrainian customs territory, as well as the procedure for paying for the services of international donor registries of HSCs for the search for histocompatible donors abroad, for receiving, verifying and processing grafts, as well as for their delivery to Ukraine.

In general, the regulatory framework of Ukraine in the field of HSCT needs to be improved in order to eliminate gaps, shortcomings and contradictions, as well as to specify certain provisions and terms. In its turn, the absence of a unified terminology and clear legal regulation negatively affects the development of HSCT system in Ukraine, as it creates significant organizational and legal problems that hinder the development of the industry as a whole and may cause legal conflicts in the future.

In order to improve efficiency and regulatory support of activities related to HSCT in Ukraine, it is appropriate:

1. To introduce into the terminology of the Law of Ukraine «On Transplantation» and other normative legal documents instead of the term «bone marrow» the term «hematopoietic stem cells» with the description of their source: «HSCs of bone marrow», «HSCs of peripheral blood», «HSCs of cord blood».

2. To create and ensure the proper functioning of the unified state information system of transplantation provided by the Law of Ukraine «On transplantation of organs and other anatomical materials to a person», as well as the effective work of the already established Ukrainian register of donors of hematopoietic stem (bone marrow) cells of the Ministry of Health of Ukraine.

3. Develop and implement national legal documents on the quality and safety of donation, collection, evaluation, processing, preservation, storage, transportation and distribution of HSCs from various sources (peripheral blood, bone marrow and umbilical cord blood), which are unified with the relevant international and European standards (EU Directives 2004/23/EC, 2006/17/EC and 2006/86/EC).

4. To develop:

- 4.1. Regulation on the Register of HSCs Donors of in Ukraine.

- 4.2. The procedure for compensation to HSCs donors related to donation.

- 4.3. The procedure for state insurance of living donors of homotransplants in case of death of a donor, infection, the emergence of other illnesses or health disorders related to donation, as well as the procedure for compensation for diseases or health hazard related to donation, including additional expenses for treatment, enhanced nutrition and other measures aimed at social, work and professional rehabilitation.

- 4.4. The procedure for import and export of HSCs transplants from Ukrainian customs territory.

- 4.5. The order of payment for services of international HSCs donor registries for the search for histocompatible donors abroad, collection, evaluation and processing of transplants, as well as their delivery to Ukraine.

CONCLUSION

1. An analysis of the regulatory documents of the EU and a number of leading countries in the world that regulate the production and circulation of human cells, tissues and their products for therapeutic purposes, including HSC, to human indicate that they are based on WHO guidelines and recommendations, provisions of the Convention on the Protection of Human Rights and Dignity of the Human Being on the Application of Biology and Medicine: the Convention on Human Rights and Biomedicine, The Additional Protocol to the Convention on Human Rights and Biomedicine on the Transplantation of Human organs and tissues, as well as other documents on the quality and safety of organs, tissues and cells.
2. Principles of regulation of the production and circulation of human cells, tissues and products on their basis, including HSCs transplantation, have their own specifics, in contrast to regulatory approaches to organ transplantation. HSCs from bone marrow, peripheral and umbilical cord blood, as a rule, are regulated by legal acts separate from organs transplantation. As an exception, in the US, the NOTA defines «bone marrow» as an organ, and the peripheral and umbilical cord blood stem cells fall under the definition of «human cells, tissues and products on their basis» therefore, are regulated by FDA separately from the bone marrow.
3. The general principles of regulation of the production and circulation of human cells, tissues and products based on them, including HSCs for transplantation, are based on a multilevel approach that takes into account the potential risks of their use. Risk-based regulation implies that the level of regulatory control should be proportional to the level of risk.
4. As a rule, autologous and allogeneic HSCs for «normal» transplantation, which during the production process underwent minimal manipulations and intended for homologous use (restoration of hematopoiesis), are defined as low-risk products. However, there are exceptions. For example, the FDA in the United States refers HSCs from unrelated donors for allogeneic transplantation to high-risk products.
5. HSCs that underwent more than minimal manipulations and/or intended for non-homologous use are identified as high-risk products.
6. To manage the low-risk products group, emphasis is placed on the need to prevent the transmission and spread of infectious diseases from donors to recipients, as well as to ensure the safety and quality of human tissues and cells in the process of their collection, processing, storage and distribution for application. For a high-risk group, it is also necessary to demonstrate to the regulating body the safety and efficacy of human tissues and cells for their use by humans, and to obtain permission from the regulatory body for their use in humans prior to marketing. The high-risk group is regulated by the legislation for biological products, medicines and/or medical products that requires compliance with the GMP rules and obtaining a marketing authorization.
7. The requirements for the quality and safety of cell therapy, including the bone marrow, peripheral and umbilical cord blood developed by international professional organizations (ACHTA, FACT, JACIE, WMDA, Netcord, AABB), comply with the requirements of the relevant EU, US, Canada and Australia legal acts for HSCs, which have undergone minimal manipulations and intended for homologous application.
8. Today in Ukraine, in the field of HSC, there is no legislative regulation similar to that applied in the leading countries of the world. The existing legislative and regulatory framework mainly regulates activities related to organ transplantation, and does not take into account the specifics and features of HSC, and therefore is imperfect, fragmented and partially effective.
9. Participation in the transnational HSCs transplant exchange system provide that Ukraine needs to improve and harmonize national legal framework regarding quality and safety for donating, collecting, testing, processing, preserving, storage, transporting and distributing HSCs from different sources (peripheral blood, bone marrow, and umbilical cord blood) with its relevant international and European standards (EU Directives 2004/23/EC, 2006/17/EC and 2006/86/EC).

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