

## Guideline

# Draft of Iranian National Guideline for Cell Therapy Manufacturing

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### Abstract

Cell therapy, a promising method for treatment of incurable diseases, has been moving fast from basic research laboratories to clinical practice in recent years. Defining clear and strict regulations for manufacturing of cell therapy products in clinical applications is the best way to give assurance to the public sector for safe usage, harmonizing research projects, and placing barriers for unqualified products from entering this market. To achieve this goal, the Iranian Council for Stem cell Science and Technologies sponsored a project in 2013 to develop a national cell therapy guideline for research and clinical trials. To prepare the preliminary guideline, a comprehensive literature and document review was performed by an expert team. The draft was subsequently revised and approved in May 2014 by a large group of experts who were practically involved in basic and clinical fields of regenerative medicine. The final guideline covered all aspects of cell manufacturing, including ethical issues, manufacturing process, quality controls, transportation, harvesting, storage, and release of cell-based products. The optimal infrastructure of the cell manufacturing facility as well as the eligibilities of man-power working in the facility were also described. After adoption in the Council, the guideline was sent to the Ministry of Health and Medical Education for confirmation and final approval. In this report, we introduce the main topics and mention some of the important items of this guideline. The complete draft of the guideline is available as a supplement in this issue.

**Keywords:** Guideline, Cell-based Therapy, Regenerative Medicine

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## Introduction

Productive knowledge on stem cell and cell-based therapies has resulted in tremendous progress in medicine and established a cornerstone for regenerative medicine which highlights a bright and hopeful perspective for treatment of incurable diseases in near future.

In recent years, investigators of the Islamic republic of Iran have made significant advances in scientific publications and practical achievements in cell production technologies as well as other fields of regenerative medicine.<sup>1</sup> Several laboratories have been developed to cover research requisites and university-based good manufacturing practice (GMP) facilities have been established to commence application of research products in clinical trials. A survey in 2011 reported 33 registered cell-based clinical trials and 21 cell therapy articles published from the Islamic republic

of Iran.<sup>2</sup> At the end of July 2016, there were 15 cell therapy trials registered in the Iranian Registry for Clinical Trials.<sup>3</sup>

In 2009, the Iranian Council for Stem Cell Sciences and Technology (ICST) was established by vice presidency for science and technology to foster and harmonize various scientific and therapeutic activities under a national science and technology development roadmap. A national document for Stem cell and Regenerative Medicine was prepared in 2012 and adopted by the president in 2013. In December 2013, ICST sponsored a project to prepare the first national guideline for cell therapies. This report is an abstract of the final report of that project which has been adopted as the national guideline in the council.

## Materials and Methods

An executive team comprising of five technical experts carried out a comprehensive study to find and collect relevant literature, guidelines and standards in the field of cell therapies and clinical grade cell manufacturing. Banking and usage of hematopoietic stem cells from any resource, including umbilical cord and bone marrow for use in hematopoietic stem cell transplantation, organ and tissue transplantation, blood and blood-derivate transfusion, and *in vitro* fertilization (IVF) were excluded from the scope. The collected references were reviewed and the topics of interest were defined. Annex 1 in the supplement demonstrates the references which were used for writing the final draft. The draft of the guideline was prepared in accordance with “human tissue banking standards” approved by the Iranian Food and Drug Organization

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(IFDO) in the Ministry of Health and Medical Education.

The final draft was circulated in a group of experts consisting of basic scientists, clinicians, policy makers, ethicists, and regulatory bodies. After three months, the invited individuals (Annex 2) convened in a two-day meeting to share their comments and finalize the guideline. The purpose of the meeting was to identify and discuss scientific considerations and challenges for development of human cell-based products subjected to clinical application and premarket approval. Based on the existing evidence, they tried to cover the main concerns and questions of the manufacturers and clinicians in procurement, processing, transportation, and prescription of cell therapy products.

The final draft was prepared and adopted by the council and sent to the Ministry of Health and Medical education for final approval in November 2014.

## Results

The complete draft of the guideline has been published as a supplement in this issue. The main topics which have been discussed in the guideline are as follows:

- Structure of cell processing centers and cell banks
- Ethical and legal regulations
- Coding and traceability
- Cell and tissue recovery and transport
- Processing and production of cell products
- Storage and transport
- Cell transplantation and post transplantation surveillance
- Quality assurance and quality management system
- Documentation
- Environmental Health and safety

### Structure of cell processing and cell banking centers

Each center should prepare and declare its goals, visions, and missions complying with the national rules. Based on the specific activity of the center, two groups of specialists are necessary as advisory board and executive board. The executive members should be qualified individuals who would act as executive manager, medical director, quality control manager, and technical staff. The characteristics and expertise of these individuals have been defined.

The processing environment must have enough space, and appropriate design and location for the main activities. It must be divided into areas with enough space to prevent labeling mistakes, contaminations, and cross-contaminations during quarantine, storage, release, or distribution. Except for the processes performed in closed systems, all open procedures must be performed under class II microbiological safety cabinet (class 100) which is placed in a clean room. It is recommended that the buffer area for cell processing be set at class 10000.

The centers must have documented work instructions for maintenance, cleaning, and decontamination of clean rooms and its equipment on daily, weekly, and monthly bases. In addition, the processing centers must be carefully designed to reduce the potential harmful risks for the staff, donors, and recipients. To reduce the risk of contaminations during cell production, several points have been described in the guideline according to the accepted general rules regarding aseptic techniques and clothing in the clean rooms.

### Ethical and legal regulations

It is necessary to be assured of the efficacy and safety of the cellular products *in vitro* and in animal models. Any financial deal between the donor and the recipient and the researchers is prohibited.

Before taking informed consent from the patients, broad information about the cell therapy should be given adjusted to the level of education and language of the patients. The information should include the aims of the project, potential benefits and risks, process of donation, all stages of the intervention and trial, lab tests that will be carried out, and other common ethical issues.

Files containing personal information of participants must be kept confidential with the most comprehensive protective tools.

Cell-based clinical trials should be planned only if superior outcomes are expected compared to current therapies. The project should be approved by an expert committee responsible for reviewing and auditing clinical trials in this area. It is recommended to register the trial information in the Iranian Registry of Clinical Trials (WWW.IRCT.IR) before starting the study and after obtaining ethical approval.

### Cell and tissue recovery and transport

Donor eligibility form must be signed and registered by an authorized physician through taking detailed medical history and careful physical examination. The following tests should be performed on the donors' samples in order to prevent any harms and unwanted outcomes for recipients and the staff: Human Immunodeficiency Virus types 1 and 2, Hepatitis B Virus, Hepatitis C Virus

In case of allogeneic cell therapy products, tests for syphilis should also be performed. In some regions of northeast of Iran which are endemic for Human T Cell Lymphotropic Virus (HTLV), tests for HTLV1 and 2 are necessary. According to the national regulations for blood transfusion and organ transplantation, a few additional tests may be considered for autologous or allogeneic cell transplantation.

The organization must have written work instructions for recovery process, storage, transportation, package, monitoring, cleaning, decontamination, and sampling. Cell and tissue recovery center must have all necessary facilities defined by authorities from the Ministry of Health and Medical Education and should observe all recommendations defined for packaging, labeling, shipment, and transport of the biological samples.

### Cell processing and production

In general, the risk of clinical adverse effects is higher for transplantation of cells with higher proliferation potency, lower developmental stage, and more *ex vivo* manipulations.

It is recommended to refrain from using animal-derived materials for clinical grade cell manufacturing; however, when suitable alternatives are not accessible, the safest preparation of these products should be used. Materials and reagents which are used for cell manufacturing must be of clinical or GMP grade.

Before releasing the final product for transplantation or storage, the following tests must be performed: cell counting and viability, gram staining, routine microbial culture, endotoxin assay, and mycoplasma detections.

For cell tracking in human clinical trials, the safest cell labeling before transplant and harmless detection methods after transplantation must be used. MRI is preferred due to its

higher safety and resolution, unrestricted penetration power, and capability for imaging soft tissue and anatomic borders.

#### Storage and release

For cell banking, Dimethyl sulfoxide (DMSO) as cryoprotectant and storage in vapor phase of liquid nitrogen are recommended. Frozen samples must be transported in liquid nitrogen container or on dry ice. Unfrozen samples must be transported at a temperature between 1 to 10°C as soon as possible.

Transplantation must be performed by a skilled team under supervision of a specialist (MD) in the relevant field. The physician in charge of transplantation is liable for predicting and managing potential unwanted side effects of the transplantation.

The number of cells for transplantation, intervals of transplantation, sample size, and the route of administration must be based on recent scientific evidences. A series of examinations and follow-up must be conducted to assess the potential side effects and efficacy of the transplantation, depending on the disease, conditions of the patient, type of transplanted cells and the method of transplantation. The follow-up program must be determined according to the latest scientific evidences and the PI is responsible for this.

In case of any unwanted side effects during or after transplantation, all units involved in acquisition, processing, distribution and transplantation of the product must be informed quickly. A written report of probation of side effects and amendatory acts must be sent out to the competent authorities.

#### Coding and traceability

To prevent incorrect labeling of cellular products exact labeling procedures are discussed under this topic referring to the guideline of IFDO.

#### Quality assurance and quality management system

International standards and guidelines exist for implementation of quality management systems in organizations (irrespective of their scopes) which provide a good framework for cell processing and cell therapy centers. ISO 9001 and ISO 13485 and GMP are amongst the most widely used standards for implementation of quality management systems. The major elements of the quality management system include: Organizational structure and responsibility chain in the organization, Documentation, Control of the process, Methods of determination, correction and prevention of quality errors. Finally the center should have a program for risk management to define risk planning, risk identification, qualitative and quantitative analysis of the risk, risk response and monitoring the effectiveness of risk management.

#### Documentation

All processes applied in the organization must be documented in a clear, comprehensive, confidential non-erasable, and retrievable archive. Each organization must define the list of required documents according to the type of activity and the quality requirements. These documents must contain at least the following: Organization chart, job descriptions, accountability chain of the organization, eligibility criteria for job positions. Standard operational procedures (SOP) must be documented to comply with the minimum standards recommended by professional associations and national or regional regulations. These SOPs should address donor eligibility criteria, properties

of the materials used, characteristics of the equipment and storage system and environmental conditions. All methods applied for quality control, and instructions for labeling and release should be recorded. In addition, the process for reporting side effects and corrective actions, traceability, recall of nonconforming products, and recipient follow-up must be described.

#### Environmental health and safety

Environmental surveillance systems must be defined as a SOP to be capable of proving a safe working space in compliance with current national regulations. There must be a defined SOP for safe disposal of waste in the organization and all processes related to waste disposal should be done in compliance with this SOP. This process must be in compliance with national regulations of medical waste disposal.

## Discussion

Many regenerative medicine therapies are approaching market authorization. In parallel, public sectors have been pursuing the advances in this field with immense interest with a general belief that stem cell therapy would offer a magical treatment for incurable or hard-to-treat diseases. In this situation, special care should be taken to prevent undesirable effects of stem cells regarding pseudoscientific and misconducted activities. Physicians and medical researchers are expected to adhere to minimal requirements and criteria for good clinical and manufacturing practice (GCP and GMP) in all procedures and products related to cell-based therapies. Therefore, careless and inappropriate design of research projects renders the results unreliable and may produce negative drawbacks in the community and medical society. One of the best ways to reduce these concerns is to develop a practical and descriptive guideline which covers all aspects of cellular therapies regarding professional and ethical priorities. Such a framework can fulfill clear criteria for conduction and implementation of research projects for researchers on the one hand, as well as assessment and audit of therapeutic interventions for regulatory bodies, ethical committees, and policymakers on the other.

The EU has a regulation for Advanced Therapy Medicinal Products (ATMPs) which connects the authoritative instructions of medicinal devices (93/42/EEC) and medicinal products (2001/83/EC).<sup>4,5,6</sup> ATMPs include tissue engineered, cell therapy and gene therapy products. They also developed a Committee for Advanced Therapies (CAT) to assess marketing authorization applications of ATMPs in Europe which provides specific scientific expertise to support applicants.<sup>7,8</sup>

The key principles of the ATMP regulation for products are: no marketing without prior authorization, demonstration of quality, safety and efficacy, postauthorization vigilance and a centralized review procedure.<sup>8</sup>

The EU has also published several guidelines on cell-based and gene therapy medicinal products as well as risk-based approach in advanced therapy medicinal products, and good clinical practice which are available online.<sup>9-13</sup>

The ISSCR is an independent non-profit organization that aims to make an international platform for communication and education in the emerging field of stem-cell research and regenerative medicine. ISSCR published the first guideline for embryonic-stem-cell research in 2006.<sup>14</sup> The society developed the second guideline for clinical translation of stem-cell research in 2008

which articulated core ethical principles for guiding both basic and clinical stem cell research.<sup>15</sup> That guideline was updated in 2016 which encompasses a broader scope of research and clinical endeavor covering generally of regulatory practice, the cost of regenerative medicine products, and public communication mostly from ethical, social points of view.<sup>16,17</sup> Although these guidelines describe some general rules and useful hints on cell processing and production, they do not cover all requirements of GMP compliant cell manufacturing.

Researches in Phase II and III trials using various cell-based products are growing worldwide.<sup>18</sup> Encouragingly, regulators and healthcare payers have cautiously opened discussions about collaborative support of some of these clinical trials while protecting both patients and budgets.<sup>8</sup>

Clinics that offer various cell therapies for different diseases have been established throughout the world, both in newly industrialized countries such as China, India, and Mexico and in developed countries such as Japan, the United States, and some European countries.<sup>19</sup> Some of these countries have announced their own regulatory guidelines.<sup>20</sup>

In this report, we briefly described the draft of Iranian guideline for cell therapy products. The main goals of this guideline are to improve the quality of cell-based clinical trials and define the basic rules for clinical grade cell manufacturing. It includes all steps of acquisition, transportation, banking and administration of stem and somatic cells and their derivatives and covers the minimum requirements for clinical use of cellular products. Large cell processing and manufacturing centers may follow higher standards which may have not been addressed in this guideline. It is worthy to mention that due to rapid advancement of knowledge and technologies in this field, reflections of experts' views on new achievements in cell preparation and safety issues are welcome to update this guideline in next editions. The ICST has been pursuing the approval process and acts in concert with the IFDO to release the final adopted guideline in near future.

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