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Review

Scientific considerations for the regulatory evaluation of cell therapy products☆

John Petricciani [a, *], Takao Hayakawa [b], Glyn Stacey [c], Jean-Hugues Trouvin [d], Ivana Knezevic [e]

[a] International Alliance for Biological Standardization (IABS), Switzerland
[b] The Chemo-Sero-Therapeutic Research Institute and Kindai University, Japan
[c] National Institute of Biological Standards and Control (NIBSC), Medicines and Healthcare Products Regulatory Agency (MHRA), UK
[d] Paris Descartes University, France
[e] World Health Organization, Switzerland

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ABSTRACT

Cell therapy involves the administration of a viable somatic cell preparation to a patient for the treatment of a disease or traumatic damage. Because cell therapies are complex and very different from traditional biological products, they present significant challenges for regulatory authorities, manufacturers, developers, health care providers, and patients involved in their application. Like other emerging areas of biomedical research and development, there are many issues where regulatory views and decisions among countries and regions may differ due to minimal scientific evidence to support safety and efficacy, and lack of experience with these novel treatments. A brief overview of the current regulatory landscape for cell-based therapies is presented, and the need for a global effort to develop a set of common principles that may serve to facilitate the regulatory evaluation and market availability of these products is identified. In addition, a number of elements that could form a core consensus package of requirements for evaluating human cell therapy products is presented in the supplemental material which should be read in conjunction with the manuscript.

1. Introduction

Regenerative medicine, which includes cell therapy (CT), holds great promise for the provision of treatments for diseases and trauma not previously possible using traditional approaches. However, it encompasses a very broad range of developing products and therapies that can engage the use of cells, rDNA tissue engineering constructs and biotherapeutic medicines possibly in combination, which presents a significant and now rapidly developing challenge for the assurance of consistent and safe approaches to making such products available for the improvement of global public health.

CT involves the administration of a viable somatic cell preparation, appropriately processed, to a patient for the treatment of a disease or traumatic injury. Cell therapy products (CTPs) are complex in their structure, content, mode of action, and delivery, all of which create significant challenges for regulatory authorities, manufacturers, and health professionals.

There is substantial diversity among CTPs based on product origin, target disease, target patients, the intended patient population and their specific needs for new therapies, application sites, application methods, and cell processing methods (Fig. 1). Therefore, the details of both the CTP nonclinical and clinical testing programs will depend on product-specific features and their clinical use.

Some of the crucial differences between CTPs and other biological medicines are that the therapeutic cells:

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* Corresponding author. POB 1925, Palm Springs, CA 92263, USA.
E-mail addresses: petriccianiIABS@aol.com (J. Petricciani), takao-hayakawa@mtg.biglobe.ne.jp (T. Hayakawa), glyn.stacey@nibsc.org (G. Stacey), jean-hugues.trouvin@parisdescartes.fr (J.-H. Trouvin), knezevici@who.int (I. Knezevic).

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Abbreviations

ATMP	advanced therapy medicinal products
BLA	biologics license application
BMT	bone-marrow transplantation
CT	cell therapy
CTP	cell therapy product
EDQM	European Directorate for the Quality of Medicines and HealthCare
EMA	European Medicines Agency
FDA	Food & Drug Administration (USA)
GCCP	Good Cell Culture Practice
GMP	good manufacturing practices
IABS	International Alliance for Biological Standardization
JST	Japan Science & Technology Agency
MFDS	Ministry of Food and Drug Safety (Korea)
NCL	national control laboratory
NRA	national regulatory authority
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
SC	stem cell
SCL	stem cell line

- may survive in the tissue potentially for the life time of the recipient
- respond to their environment and interact with other cells and humoral factors in ways which are not encountered with other medicines
- may have the capacity to replicate or to mature *in vivo* thus evolving their functionality after they have been administered to the patient
- may migrate and distribute in tissues or organs other than the one intended

These factors have a significant impact on notions of potency, dose and safety which may need to be considered on a case by case basis for new therapies.

The field of CT has advanced rapidly during the past decade, and products already have been approved in several countries. Among the first CTPs was Carticel® (autologous cultured chondrocytes) which was approved by the USA Food & Drug Administration (FDA) in 1997 for the repair of clinically significant, symptomatic cartilaginous defects. Since then, technology breakthroughs and research advances have led to increasing expectations that novel cell-based investigational products will become useful new therapies. Nevertheless, it remains an emerging area of biomedical research and development in which there are many areas of regulatory uncertainty and differences among countries and regions.

Added to these challenges is the fact that many cell therapies are being developed by smaller private enterprises, academic institutions, or health-care institutions with limited resource for planning a full product life-cycle. In addition, many such institutions have very limited regulatory experience and support. Thus, regulators will need to engage early with these product developers to facilitate the safe and effective progression of potential new CTPs to market.

An additional challenge relates to the specific pharmaceutical pathway for autologous or allogeneic CTPs starting from the donor/patient (for biopsy collection) up to the manufacturing site (for production, quality controls and release) before being administered to the recipient in a given healthcare facility, taking into consideration that final cell preparation is fragile and has a limited shelf life.

A wide variety of cell types are being used for therapeutic purposes. These include: a) immune cells such as dendritic cells, T cells and NK cells; b) tissue specific cells such as fibroblasts, keratinocytes and chondrocytes; c) stem cells (SCs) (e.g. hematopoietic stem cells to be used in a heterologous recipient; d) stem cell-derived preparations such as those prepared from stem cell lines – SCLs; e) cells combined with extra-cellular matrix or scaffold; and f) encapsulated cells. Tissue sources of autologous, allogeneic or even xenogeneic origin used in or proposed for cell therapy include: adipose tissue, bone marrow, brain, buccal epithelium, embryo, eye, heart, placenta, peripheral blood, skin, liver and umbilical cord (Fig. 1). From a clinical perspective, cell therapies have been categorized according to the level of manipulation they have undergone, depending on the various clinical perspectives, ranging from simple bone marrow transplantation to complex tissue engineering (Table 1).

- *Minimally manipulated cell* therapies include, for example, hematopoietic stem cells for transplantation (bone marrow

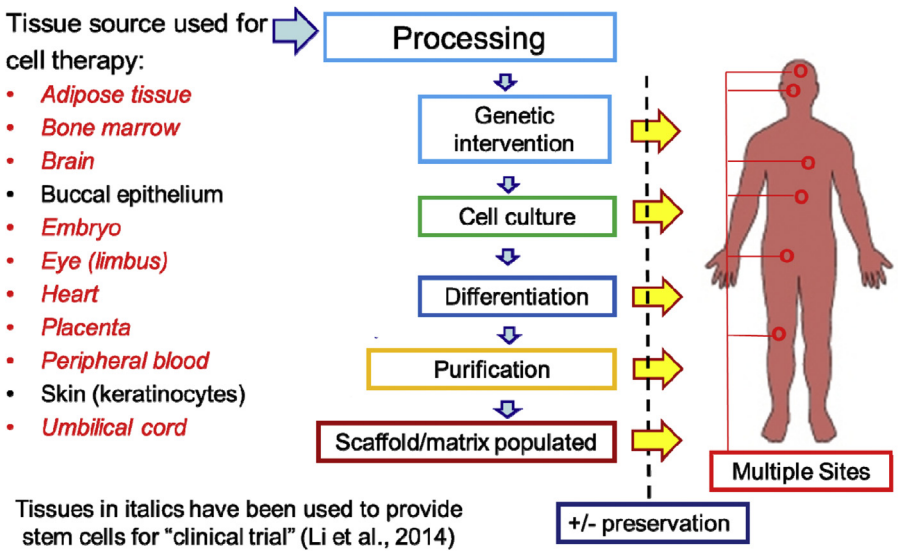

Fig. 1. Examples of the numerous elements that may make up a cell therapy manufacturing process.

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