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Review

Comparison of international guidelines for regenerative medicine: Knee cartilage repair and replacement using human-derived cells and tissues

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ABSTRACT

Regenerative medicine (RM) is an emerging field using human-derived cells and tissues (HCT). Due to the complexity and diversity of HCT products, each country has its own regulations for authorization and no common method has been applied to date. Individual regulations were previously clarified at the level of statutes but no direct comparison has been reported at the level of guidelines. Here, we generated a new analytical framework that allows comparison of guidelines independent from local definitions of RM, using 2 indicators, product type and information type. The guidelines for products for repair and replacement of knee cartilage in Japan, the United States of America, and Europe were compared and differences were detected in both product type and information type by the proposed analytical framework. Those findings will be critical not only for the product developers to determine the region to initiate the clinical trials but also for the regulators to assess and build their regulations. This analytical framework is potentially expandable to other RM guidelines to identify gaps, leading to trigger discussion of global harmonization in RM regulations.

1. Introduction

Regenerative medicine (RM) is an emerging filed using human-derived cells and tissues (HCT). The number of HCT products approved worldwide is still limited; however, technological innovation has improved the quality of HCT products, which will eventually develop into a new stronghold of the healthcare industry. Repair or replacement of knee cartilage is one of the major targets of HCT products approved worldwide. Carticel (Genzyme), Chondrocelect (TiGenix), MACI (Genzyme), and JACC (Japan Tissue Engineering Technology) have been approved in the USA, EU, and Japan respectively [1] but this approval is restricted to their respective region. To maximize the return from investment, multiregional approval will be an issue for the developing entities. Global development of HCT products has certain limitations from the technical perspective, such as typically short shelf-life of the products, logistical issues related to the cold chain and challenges regarding control of HCT mass-production. Additionally, the regulatory framework is different in each country, making product development more challenging [2]. In the United States of America (USA), HCT products are regulated by the Food and Drug Administration (FDA). The HCT products will be assessed as cellular and gene therapies, tissues therapies, medical devices or combination products, depending on the origin of the cells and primary mode of action [3]. In the European Union (EU), the European Medicine Agency (EMA) designates RM products as Advanced-therapy medicinal product (ATMPs), which are the comprehensive category covering somatic cell therapies, gene therapies and tissue therapies [4]. In Japan, RM products were recently defined, in 2014, in the Pharmaceuticals and Medicinal Devices Act, including the concept with cellular therapies, medicinal devices and gene therapies. These products are reviewed by the Pharmaceuticals and Medical Device Agency (PMDA) and approved by the Ministry of Health, Labor and Welfare (MHLW) [5]. As HCT products are not defined in the same context, a comparison of guidelines from each country in the same context is challenging; this is one of the hurdles to the development of RM products in a harmonized manner across the world. Local definitions for RM products have been previously reported [6] but not in detail at the level of guidelines. In this paper, the authors present an analysis of the guidelines for HCT products developed for knee cartilage repair/replacement, using a new

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Abbreviations

ATMP	Advanced-therapy medicinal product
CFR	Code of Federal Regulation
CMC	Chemistry, manufacturing and control
EMA	European Medicines Agency
ES	Embryotic stem
FDA	U.S. Food and Drug Administration
HCT	Human-derived cells and tissues
IDE	Investigational device exemption
IND	Investigational new drug
iPS	Induced pluripotent stem
MHLW	Ministry of Health, Labor and Welfare
OMDE	Office of Medicinal Devices Evaluation
PFSM	Pharmaceutical and Food Safety Bureau
PMDA	Pharmaceuticals and Medical Devices Agency
RM	Regenerative medicine
SC	Somatic cell
SSC	Somatic stem cell
USP	U.S. Pharmacopeia

analytical framework to identify differences in the regulatory jurisdiction at the level of guidelines. This is the first report to compare multi-regional guidelines for HCT products for knee cartilage repair/replacement.

2. Materials

In this study, we selected similar guidelines for products used to repair/replace human knee cartilage. Corresponding products have been approved in all regions, suggesting that all regional agencies are experienced in the review of this type of product. The guidelines and related information are listed in Table 1. Carticel is the first related product approved in the world without any specific guideline for products used to repair/replace knee cartilage.

3. Methods

To compare regional guidelines based on different regulatory concepts, a new framework that is independent from the local definition is required. In this study, the contents of the guideline were analyzed by 2 indicators, product type and information type.

3.1. Product type

Product types mentioned in the guidelines were categorized into 19 types, based on combinations of following categories:

1. The origin of cells: autologous or allogenic
2. The type of cells: somatic cells (SC), somatic stem cells (SSC), induced pluripotent cells (iPS), embryotic stem cells (ES), and non-human cells
3. Manipulated or non-manipulated
4. Medicines or medical devices

The definition of manipulation is generally common in the USA, EU, and Japan, where techniques such as artificial cell culture, enzymatic digestion, differentiation, and gene modification are regarded as manipulation. On the other hand, cell sorting, washing, freezing, and thawing are not regarded as substantial manipulation. Medical devices are variously defined in the local regulations but in this paper, products with a 3-dimensional physical structure are categorized as medical devices, while others are categorized as medicines. Theoretically impossible combinations such as “autologous ES cells”, “non-manipulated medical devices”, or “non-manipulated iPS cells” were not included among the 19 product types. All 19 combinations are listed in Table 2.

3.2. Information type

The information required in the guidelines was categorized into 5 types, based on general terms used in the assessment of medicines: non-clinical, clinical, CMC (chemistry, manufacturing and control), post approval, and procedures. Non-clinical information includes non-human experimental data such as the animal study, toxicology study, pharmacology study etc. Clinical information describes information such as clinical trial design, end-point, and patient population. CMC information is related to the quality of the product such as raw materials, release and stability tests and manufacturing process. Post approval category contains the requirements such as follow-up study and pharmacovigilance. Procedural information is related to the tutorial of regulatory documentation and submission for the developers.

4. Results

4.1. Results of the categorization by product type

The Japanese guideline, “Points to consider for the evaluation of specific products: Articular cartilage repair” [7], clearly regulates both, medicines and medical devices that contain manipulated, human-derived chondrocytes (somatic cells) and mesenchymal stem cells (somatic stem cells); however, it does not regulate human ES, human iPS, and xenogeneic cells. In Japan human ES and human iPS cells derived products are regulated by other general guidelines [10–12] but there is no guideline regulating xenogeneic cells derived product.

The guideline in the USA is “Guidance for industry: preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage” [8]. The scope of the guideline is described in the first

Table 1
List of guidelines for products used to repair/replace knee cartilage and related information.

Country	Guidelines and related information
Japan	Points to consider for the evaluation of specific products: Articular cartilage repair (OMDE Director notice 1215 No.1) [7] Draft issued: June 2010; finalized: December 2011 Related Product: JACC (J-TEC, approved in July 2012)
USA	Guidance for industry: preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage [8] Draft issued: July 2007; finalized: December 2011 Related product: Carticel (Genzyme, approved in August 1997)
EU	Reflection paper on *in vitro* cultured chondrocyte containing products for cartilage repair of the knee [9] Draft issued: September 2009; finalized: April 2010 Related product: ChondroCelect (TiGenix, approved in October 2009), MACI (Genzyme, approved in June 2013)

IDE: investigational device exemption; IND: investigational new drug application; OMDE; office of medical devices evaluation.

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