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Cell-based product classification procedure: What can be done differently to improve decisions on borderline products?

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Abstract

In June 2015, European Medicines Agency/Committee for Advanced Therapies (CAT) released the new version of the reflection paper on classification of advanced therapy medicinal products (ATMPs) established to address questions of borderline cases in which classification of a product based on genes, cells or tissues is unclear. The paper shows CAT's understanding of substantial manipulation and essential function(s) criteria that define the legal scope of cell-based medicinal products. This article aims to define the authors' viewpoint on the reflection paper. ATMP classification has intrinsic weaknesses derived from the lack of clarity of the evolving concepts of substantial manipulation and essential function(s) as stated in the EU Regulation, leading to the risk of differing interpretations and misclassification. This might result in the broadening of ATMP scope at the expense of other products such as cell/tissue transplants and blood products, or even putting some present and future clinical practice at risk of being classified as ATMP. Because of the major organizational, economic and regulatory implications of product classification, we advocate for increased interaction between CAT and competent authorities (CAs) for medicines, blood and blood components and tissues and cells or for the creation of working groups including representatives of all parties as recently suggested by several CAs.

Key Words: *accessibility, blood cell transfusion, cell-based borderline products, cell-based medicinal products, cell transplantation, classification procedure, essential functions, regulation, substantial manipulation, sustainability*

Introduction

The term "cell-based product" comprises a broad variety of products including several categories of advanced therapy medicinal products (ATMPs), cell and tissue transplants and blood cell transfusions, among others.

In this article, we center our attention on the classification of cell-based borderline products—defined as products that might fall between two or more regulated product categories, as is the case of lymphocyte immunotherapy—highlighting the vague line among some ATMPs, blood products and cell transplants in contrast with the enormous consequences affecting

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product development in light of these classification decisions.

According to European legislation [1,2], a cell-based product is an ATMP when it has been substantially manipulated so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered and/or when the cells or tissues are not used for the same essential function or functions in the recipient as in the donor. The distinction between somatic cell therapy medicinal products (SCTMPs) and tissue-engineered products (TEPs) depends on the mechanism of action. In the case of SCTMPs, the cells or tissues exert a pharmacological, immunological or metabolic action, whereas TEPs are used for regeneration, repair or replacement.

The legal criteria to establish what is or is not a cell-based medicinal product may give rise to different interpretations because of the evolving nature of scientific knowledge and because, in our view, the concepts of "substantial manipulation" and the "same essential function(s)" are difficult to interpret. Nevertheless, the decision of classifying a borderline cell-based product as an ATMP or otherwise has important consequences because of the differences in the requirements for its processing and product development pathway (Table I), making this an issue of crucial importance.

The donation, procurement, testing, traceability and coding activities for cell transplantation have to comply with the standards and requirements set out in several Directives and Commission Directives [3–6]. Similarly, the collection, testing and traceability activities for blood cells intended for transfusion must comply with standards of quality and safety of human blood and blood components regulated at European level [7–9]. In the case of ATMPs using cells, tissues, human blood or blood components as starting materials, the same European legislation is applicable for their donation, procurement or collection, testing and traceability as established in Regulation 1394/2007 [2] and Commission Directive 2009/120/EC [1].

As for processing, irrespective of the investigational or approved status of the product, medicinal products require Good Manufacturing Practice (GMP) compliant facilities and the principles of GMP must be followed [10]. For cell or tissue transplants, their processing must be performed in tissue establishments complying with the requirements set out in Commission Directive 2006/86/EC [5], which implements Directive 2004/23/EC [3]. Blood cells for transfusion must be processed in authorized blood establishments according to the requirements established in Directive 2005/62/EC [11], which implements Directive 2002/98/EC [7]. The differences in terms of costs are significant because the facilities and manufacturing requirements for medicinal products are considerably more expensive and time consuming.

Nevertheless, the biggest differences in regulation between these products are evident in the way in which they can be introduced into the clinical setting once scientific research has demonstrated their efficacy and safety. Medicinal products require a company to be granted marketing authorization under a centralized procedure through the European Medicines Agency (EMA), except in exceptional cases of hospital exemption [12]. In contrast, the different modalities of cellular transplantation and new technological developments for blood cell transfusion are included within the services offered in properly authorized hospitals or establishments under the responsibility of national or regional competent authorities (CAs). The implications in terms of economic and organizational aspects are enormous.

Table I. General requirements for cell-based products (transplants, medicinal products and transfusions) in the European Union.

	Cell transplantation	Cell-based medicinal product	Blood cell transfusion[a]
Donation, procurement or collection, testing and traceability[b]	Directives 2004/23/EC [3], 2006/17/EC [4], 2006/86/EC [5] and (EU) 2015/565 [6]	Directives applicable to cell transplant or transfusion depending on the starting materials [1,2]	Directives 2002/98/EC [7], 2004/33/EC [8] and 2005/61/EC [9]
Processing	Tissue Establishment Directive 2006/86/EC [5]	GMP Laboratory Directive 2003/94/EC [10]	Blood Establishment Directive 2005/62/EC [11]
Clinical use	1st—Clinical Research 2nd—Clinical Practice: Transplantation	1st—Clinical Trials 2nd—Marketing Authorization *Hospital Exemption*	1st—Clinical Research 2nd—Clinical practice: Transfusion

[a]Plasma derivatives do not contain cells and are mostly regulated as medicinal products.
[b]ATMPs using human cells, tissues, blood or blood components as starting materials are also regulated by cell and tissue directives and by blood and blood component directives regarding the donation, procurement or collection, testing and traceability.