Biologicals 43 (2015) 433–436

Contents lists available at ScienceDirect

Biologicals

journal homepage: www.elsevier.com/locate/biologicals

Meeting report

Regulatory landscape for cell therapy – EU view

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ARTICLE INFO

Article history:
Received 17 February 2015
Accepted 17 April 2015
Available online 19 May 2015

Keywords:
Advanced therapy medicinal products
Cell therapy
Clinical trials regulation
Committee for Advanced Therapies
European Medicines Agency
Marketing authorisation application

ABSTRACT

This article addresses regulation of cell therapies in the European Union (EU), covering cell sourcing and applications for clinical trials and marketing authorisation applications. Regulatory oversight of cell sourcing and review of applications for clinical trials with cell therapies are handled at national level, that is, separately with each country making its own decisions. For clinical trials, this can lead to different decisions in different countries for the same trial. A regulation is soon to come into force that will address this and introduce a more efficient clinical trial application process. However, at the marketing authorisation stage, the process is pan-national: the Committee for Human Medicinal Products (CHMP) is responsible for giving the final scientific opinion on all EU marketing authorisation applications for cell therapies: favourable scientific opinions are passed to the European Commission (EC) for further consultation and, if successful, grant of a marketing authorisation valid in all 28 EU countries. In its review of applications for marketing authorisations (MAAs) for cell therapies, the CHMP is obliged to consult the Committee for Advanced Therapies (CAT), who conduct detailed scientific assessments of these applications, with assessment by staff from national regulatory authorities and specialist advisors to the regulators.

1. Introduction

This is one of two articles reflecting talks given by the author at a meeting[1] in Kyoto, Japan in March 2014, the first addressing the European regulatory framework for the regulation of cell therapies and the second addressing the requirements for preclinical testing to support development of such products. The theme of the meeting was to share experience from different territories in the international regulation of such products. In particular, the meeting aimed at discussing how to ensure development of good quality, safe and effective cell therapy products throughout the world.

Harmonisation of regulatory requirements for medicinal products has been a major theme over the last 30 years with initial steps to harmonise requirements for market access taking place with the creation of the single market of the European Community in the 1980s. About this time, bilateral discussions with Japan and the US were also taking place, leading in the 1990s to major integration of the expectations of regulators in the three regions of European Union (EU), Japan and United States (US) and creation of the concept of the common technical document whereby the constituent dataset could be accepted across these three regions. Despite that the majority of the world's population is outside these territories, regulatory bodies in some other regions have tended to accept the harmonisation that has been agreed within the framework of the International Conference on Harmonisation. However, there remains scope to keep trying to agree commons standards with the purpose of reducing duplication of work. This applies also to the principles of regulation of cell products as medicinal products.

With this background, this article covers the following, as applies in the countries of the EU:

- regulation of sourcing of cells
- regulation of clinical trials
- regulation of applications for marketing authorisation
- classification of cell therapies
- other means of product supply.

In the countries of the EU, it is important to note that not one system operates, but rather that different functions operate under different regulatory systems: the reasons for this are both historical and political. In particular, the regulatory review and decision on approval or rejection of a clinical trial application is a national

Abbreviations: ATMP, advanced therapy medicinal products; CAT, Committee for Advanced Therapies; CHMP, Committee for Human Medicinal Products; EC, European Commission; EU, European Union; EMA, European Medicines Agency; MAAs, marketing authorisations.

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[1] Challenges towards sound scientific regulation of cell therapy products, March 7–8th, Kyoto International Conference Center, Kyoto Japan.

http://dx.doi.org/10.1016/j.biologicals.2015.04.004
1045-1056

competency, that is, application for a trial in a particular country leads to a decision for that country only, whereas for applications to market cell therapy products, the regulatory review and decision on approval or rejection is a pan-national competency, that is, one process leads to one decision across all EU countries. There are 28 Member States of the EU, each with their own national systems of regulation of medicinal products. In addition, the European Medicines Agency (EMA) plays a coordinating role for pooling expertise from all these countries, plus also from Iceland and Norway, in not just assessing applications for marketing of medicinal products, including all those that contain cells as their active component, but also in provision of scientific advice and support for orphan products and also paediatric drug development. The roles of the Committee for Human Medicinal Products (CHMP) and the Committee for Advanced Therapies (CAT) in this process are described below. There is a degree of complexity which, of necessity, cannot be reflected in full in this summary.

The role of the competent authority will also be discussed: this term is applied in legislation to mean those institutions within countries of the EU with responsibility for meeting obligations stated in the legislation. Thus, for a clinical trial to be conducted in a particular country with a product containing cells, application is made to the Competent Authority of that country for a decision on approval of the trial. This is separate from the role of the Ethics Committee: approvals from both the Competent Authority and from the Ethics Committee are needed in order to be able to initiate clinical testing.

Concerning oversight of sourcing the initial supply of tissue, and Ethical Review of clinical trial applications, these aspects are not dealt with in great detail here; as there is essentially no regulatory experience of the use of animal cells as human medicinal products, such products are excluded from this article.

2. Regulation of sourcing of cells

Regulatory oversight of sourcing of cells is governed in accordance with Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 [1] which addresses the requirements for quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. This covers tissues and cells intended to be subject to an industrial process to manufacture product to be given to patients: however, this Directive addresses only the sourcing and related topics of the cells, not their development as a medicinal product. Two further directives (2006/17/EC and 2006/86/EC) [2,3] provide detailed technical requirements to meet the expectations in Directive 2004/23/EC. These directives exclude blood and human organs (which are covered by other directives 2000/70/EC and 2002/98 [4,5] and by Recommendation 98/463/EC) [6] and also exclude the use of human tissue where this is within the same individual and within the same surgical procedure, with no manufacturing step. The Competent Authority under Directive 2004/23/EC need not be the same body as that under Directive 2001/83 (concerning placing a medicinal product on the market) [7]. This system of regulatory oversight of cell sourcing is nationally based with no referral to CAT, CHMP or EMA.

3. Regulation of clinical trials

Regulation of clinical trials is the responsibility of each country of the EU with each being responsible for only those trials that are proposed to take place in that country. Historically, each country in Europe had its own system of law to govern the conduct of clinical trials, sometimes, but not always, split into two parts, (A) review by an Ethics Committee and (B) review by the national Competent Authority.

Ethics Committee review addressed the welfare of subjects to be enrolled in the trial, their protection should anything go wrong, and the suitability of those conducting the trial to carry out the proposed work. In contrast, the review conducted by the Competent Authorities addressed the quality of the product to be used in the trial and whether the trial was suitably safe within the context of the scientific basis for the trial (ie whether any benefit would accrue, not necessarily to subjects within the specific trial, but from the development of the medicine for future patients).

Until the 1990s, this situation led to their being as many systems for conducting trials in Europe as there were countries, leading to major diversity in the trial review process. As a consequence of this, and anticipating further integration, EU Directive 2001/20 [8] was brought into force in the mid-2000s. Being a Directive, as opposed to a Regulation, this required national legislation to implement it in each country and from 2004, all clinical trials conducted with medicinal products in the EU have been conducted in accordance with this Directive. This Directive remains in force: however, the national implementation steps are considered to have lead to the perpetuation of differences that hindered the ease of conduct of clinical trials that take place across multiple countries. As a consequence of this perspective, steps have been taken to replace the Directive and from 2016, clinical trials in countries of the EU will be regulated by a new Regulation [9]. As a Regulation is a form of law that requires no national implementation step, this will, in practice, it is hoped, remove differences in national systems that were perceived to hinder access to the conducting of clinical trials in Europe.

Currently, the system operates such that for each country, a separate application must be made, at least one for each country where the trial is to be conducted. Most countries require two applications, one for decisions by the Ethics Committee and one for decisions by the national Competent Authority and for a small number of trials, a third review may be required eg for use of radioactive material. This need for multiple applications for the same trial in different countries results in an administrative burden which is perceived to create a competitive disadvantage in running clinical trials in the EU. In the Regulation, the principle is retained that each national Competent Authority will decide whether the trial may or may not take place in its country, although in practice, the applicant for the clinical trial will make one application to a central portal for a trial across multiple countries and will operate one process to receive the decision across all countries in which they propose to conduct the study. This system is to come into operation from 2016 and the applicant for the trial will nominate one country (the 'reporting Member State'), among those where it is proposed to run the trial, to conduct assessment of the application. The opinion of the Competent Authority of that country will be circulated to those other countries where the trial will also be run, for each national Competent Authority to consider this opinion and determine if it agrees or disagrees with it. The applicant will then be informed of the decisions of all concerned countries. In addition to this, there will also be review by a properly constituted Ethics Committee of each clinical trial application. Whereas at present, this can be entirely separate with no communication made to the Competent Authority regarding whether or not a decision has been sought or given by an Ethics Committee, under the Regulation, the system will operate such that the decision of each country will include that of the Ethics Committee and of the Competent Authority, although it remains the case that the basis of each decision is different, and the decision within each country need not be harmonised between the Ethics Committee and the Regulatory Authority; however, clearly, if either reject the application, then the