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REVIEW

Regulation of advanced therapy medicinal products in Europe and the role of academia

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Abstract

Background aims. Advanced therapy medicinal products (ATMP) are gene therapy, somatic cell therapy or tissue-engineered products regulated under (EC) No. 1394/2007 to ensure their free movement within the European Union while guaranteeing the highest level of health protection for patients. Academic good manufacturing practice (GMP) centers are major contributors in the development of ATMPs and this study assessed the impact of regulations on them. *Methods.* European academic and non-industrial facilities (n = 747) were contacted, and a representative sample of 50 replied to a detailed questionnaire. Experienced centres were further selected in every Member State (MS) for semi-structured interviews. Indicators of ATMP production and development success were statistically assessed, and opinions about directive implementation were documented. *Results.* Facilities experienced in manufacturing cell therapy transplant products are the most successful in developing ATMPs. New centres lacking this background struggle to enter the field, and there remains a shortage of facilities in academia participating in translational research. This is compounded by heterogeneous implementation of the regulations across MS. *Conclusions.* GMP facilities successfully developing ATMPs are present in all MS. However, the implementation of regulations is heterogeneous between MS, with substantial differences in the definition of ATMPs and in the approved manufacturing environment. The cost of GMP compliance is underestimated by research funding bodies. This is detrimental to development of new ATMPs and commercialization of any that are successful in early clinical trials. Academic GMP practitioners should strengthen their political visibility and contribute to the development of functional and effective European Union legislation in this field.

Key Words: *advanced therapy medicinal products, European Union, good manufacturing practice, manufacturing, regulation*

Introduction

Advanced therapy medicinal products (ATMPs) are medicinal products for human use that are based on gene therapy, somatic cell therapy or tissue engineering. A rapidly growing area in translational research, they represent the next generation of complex medicines for complex diseases and pose particular challenges to medicine regulation.

Regulation (EC) No. 1394/2007 defined ATMPs and was designed to ensure their free movement within the European Union (EU), to facilitate their access to the EU market and to foster the

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competitiveness of European pharmaceutical companies while guaranteeing the highest level of health protection for patients (1). ATMPs are regulated as pharmaceutical products, and the regulation led to the amendment of the EU Medicinal Products Directive 2001/83/EC, with Directive 2009/120/EC. Cellular starting materials are required to be procured under the national licensing structure enforcing the EU Directives 2004/23/EC, 2006/17/EC and 2007/83/EC; the Tissues & Cells Directives. All manufacturing of products require compliance with the standards of good manufacturing practice (GMP) to ensure their quality, safety and efficacy.

Academic GMP facilities are major contributors to the development of ATMPs (2). They respond to clinical needs and provide medicinal products in an environment that, albeit compliant with industrial standards, is by definition not industrial. They find themselves in a challenging position between various, sometimes conflicting, interests in the transition of ATMPs from bench to bedside. European investigator-initiated multicenter trials on ATMPs critically depend on academic GMP facilities.

The EC-funded project "The impact of Regulation (EC) No. 1394/2007 on the development of Advanced Therapy Medicinal Products (ATMPs): an academic perspective" (Grant No. 260773) was designed to assess the impact of Regulation (EC) No. 1394/2007 and the Directives on which it was based on academic manufacture and clinical trial of ATMPs. We describe one of the outcomes from the project: the results of the European survey and subsequent one-to-one interviews conducted among non-industry facilities involved in ATMPs. We determined whether specific facility characteristics are linked with success in ATMP production and development and if success is predominant in certain countries. We also investigated whether facilities believed that the regulation of these products as medicines has hindered innovation in the field.

Methods

Study design

A short questionnaire and a longer, more detailed questionnaire were constructed. The short questionnaire asked if the facilities (i) currently produce ATMPs and/or intend to produce ATMPs in the future, (ii) would be interested in establishing a network, over the next 2 years, of non-industrial GMP institutions in Europe—giving academic GMP a voice and (iii) would be willing to complete a longer, more detailed questionnaire in the near future.

To structure the longer questionnaire, in-depth discussions on prospective topics were conducted by the project consortium General Assembly with input from statisticians, most notably at the workshop "Manufacture of Advanced Therapies: Academia meets Industry" (3).

The long (and short) questionnaire(s) were in English, and it was ensured that all questions were easy to understand, with no jargon and easily translated. To avoid missing or illegible responses, tick boxes were used. The questionnaires were addressed to only one senior person per centre. The first section of the short questionnaire gave a brief overview of the survey and described its aims and objectives with a contact address and e-mail. The short questionnaire stated that there would be anonymity between centres, that is, centres would be unidentifiable when the results were reported. The study was in compliance with the Data Protection Directive (1995/46/EC) and with the Privacy and Electronic Communications Directive (2002/58/EC).

Newcastle University was responsible for the generation of the short e-mail questionnaire. The long questionnaire was designed by investigators at Newcastle University, who worked closely with Lunds Universitet (Sweden) so it could be made available electronically on the Academic GMP website. The long questionnaire included questions that asked about ATMP production/development, collaboration, facility size, consultation with regulatory bodies and opinion as regards Regulation (EC) No. 1394/2007.

Contacts for receipt of the short questionnaire were based on their affiliation with the Joint Accreditation Committee of the International Society for Cellular Therapy and European Group for Blood and Marrow Transplantation (JACIE), European Group for Blood and Marrow Transplantation (EBMT), International Society for Cellular Therapy (ISCT), Foundation for the Advancement in Cancer Therapy (FACT), European Clinical Research Infrastructures Network (ECRIN) and Committee for Advanced Therapies (CAT). Those approached also included coordinating scientists of all identified Framework Programme–funded projects related to cell therapy, stem cells, regenerative medicine and/or gene therapy, members of the UK Stem Cell Users Group and personal acquaintances.

Statistical analysis

Relationships between questionnaire responses and ATMP development and production success were assessed. The methods used included statistical inference, multiple correspondence analysis, ordinal logistic regression modeling and χ^2-based statistics. SAS (version 9.2), Minitab (version 16) and SPSS (version 19) were used for statistical analysis. The data from the telephone interviews were not subjected to statistical analysis but were used empirically to clarify responses to the questionnaires for improved interpretation of the data.