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The Regulation of Advanced Therapy Medicinal Products in Europe and the Role of Academia

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Abstract

Background: Advanced Therapy Medicinal Products are gene therapy, somatic cell therapy or tissue engineered products regulated under (EC) 1394/2007 to ensure their free movement within the European Union while guaranteeing the highest level of health protection for patients. Academic GMP manufacturing centres are major contributors in the development of ATMPs and this study assessed the impact of regulations on them.

Design and Methods: 747 European academic and non-industrial facilities were contacted and a representative sample of 50 replied to a detailed questionnaire. Experienced centres were further selected in every Member State 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.

Discussion: 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 commercialisation of any which are successful in early clinical trials.

Academic GMP practitioners should strengthen their political visibility and contribute to the development of functional and effective EU legislation in this field.

Key words

GMP (good manufacturing practice)
Regulation
ATMP
European Union
Manufacturing

Introduction

Advanced Therapy Medicinal Products (ATMPs) are medicinal products for human use, 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 medicines 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 competitiveness of European pharmaceutical companies while guaranteeing the highest level of health protection for patients¹. 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 requires 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 ATMPs². They respond to clinical needs and provide medicinal products in an environment which, 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 here 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 email. The short questionnaire stated that there would be anonymity between centres i.e. 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 email questionnaire. The long questionnaire was designed by Newcastle University who worked closely with Lunds Universitet (Sweden) in order that it could be made available electronically on the Academic GMP website. The long questionnaire included questions which 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 upon 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 (FP) - 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 modelling and chi-squared 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.

Response Rate

In total, 747 contacts in 31 European countries (25 EU Member States [MS], 4 candidate EU MS and 2 further members of the European Free Trade Association (EFTA)) were approached and were sent the short questionnaire. Of these contacts, 94 facilities (17 EU MS and 1 candidate EU MS) returned a completed questionnaire of whom 85 said they would be interested in completing the longer, detailed questionnaire. It may be argued that more advanced facilities were likely to reply, but we did see a lot of interest among those who were less advanced – these facilities wanted to improve and wished to highlight difficulties they were having with current legislation.

After distributing the long questionnaire to the interested parties, 50 completed questionnaires were received from 11 countries (of which 10 were EU MS and 1 was a candidate EU MS). The number of facilities in each of the contributing countries is shown in Figure 1.

For the majority of countries, a similar percentage of facilities from each country is observed in our sample as that which occurs in the actual population of 747 European contact points (Table 1), rendering this a representative sample chosen by proportional allocation.⁴

The remaining non-responding countries had very few facilities in the population of 747 contacts (all making up less than 2% of the total). To address the issue of non-response, telephone interviews were conducted with selected facilities.

Links with Success

The maximum number of types of ATMPs developed in a year by the facility and the maximum number of types of ATMPs produced in a year by the facility were chosen as initial indicators of 'ATMP success'. The respondent was given the opportunity to enter the number of ATMP types produced (developed) in each of several listed years. The *maximum* number of types of ATMPs produced (developed) in a year was chosen as an accurate indicator of success as (i) averaging across years may produce inaccurate results as respondents may have erroneously recorded the same ATMP as being produced/developed across several years (ii) summing across years may be inaccurate as a facility in operation over many years, producing/developing ATMPs sporadically, may have a greater grand total than a newer facility producing/developing many ATMPs in a single year. The variable measuring success therefore took an ordinal (categorical) form. Initially, in order to establish univariate associations between each question response and 'success', ordinal logistic regression was employed alongside chi-squared based statistics.

Results

The questions most significantly associated with ATMP development and production on a univariate level ($p < 0.1$) are shown in Tables 2a and 2b respectively. It is of note that there was evidence that questions 10, 37, 50 and 58 are related to both development *and* production success.

The questionnaire responses provided clear evidence that:

- Those centres which were involved in the initial development of new ATMPs were also those which successfully achieved GMP-compliant production for clinical trials. In such a novel and developing field this is to be expected and probably explains why such a high proportion of ATMP trials remain in the academic domain and have not yet progressed to industrial development. The

development phase of these cellular drugs is highly experimental and still is largely investigator-led in the EU and US. Many ATMPs in early trial are not being developed with the ultimate aim of commercial success. This relationship between development success and translation to GMP production was confirmed by the observation of the converse significant link, i.e. that those who produce know how to develop.

- It was also apparent that the centres which successfully translated to clinical trial were those which interacted with appropriate regulatory authorities for advice rather than just as part of a statutory regulatory process. This may be interpreted in one of two ways. Either the advice is essential for successful conversion to GMP and trial, or, only those centres which are already competent in GMP manufacture and trials design are confident enough to interact with their regulatory authority. Understanding these interactions was a key part the telephone interviews.

- Academic facilities experienced in ATMP development regularly pass inspections – these facilities understand how to be compliant with GMP standards and are comparable with (and potentially competitive with) industry.

- These experienced facilities mostly have a pre-existing background in manufacturing non-medicinal, minimally manipulated cell therapies (e.g. haematopoietic stem cell transplant products and associated lymphocyte infusion). They have existing quality systems for compliance with national regulation of tissues and cells and are better staffed than purely academic laboratories trying to develop ATMPs in isolation.

- It is difficult for new centres to enter the field under existing regulations because of the investment required in GMP manufacturing resources (staff and buildings). In many EU MS there remains a lack of GMP-compliant facilities in Academia that can take part in the field of translational research.

- There is a general paucity of and need for quality control programmes for qualification and standardisation of these products as they progress through development in an attempt to attain marketing authorisation in the EU and beyond.

The technique of multiple correspondence analysis^{5,6,7,8} (MCA) utilised the categorical variables most significantly associated with 'success' ($p \leq 0.05$). MCA generates a map – nearby points are similar as regards how they responded. The map can be shown multi-dimensionally. The first few dimensions are the most important - they give the best picture of the data (i.e. they account for the most variability in the data). We generate two maps – one showing which facilities are similar and the other showing which questions responses occur together (e.g. it may be the case that when a

facility replies “yes” to question A, they reply “yes” to question B – hence “QA_yes” and “QB_yes” would occur together on the plot). In this study, for both development and production, only the first two dimensions were relevant, hence 2-dimensional plots were generated. Figures 2a and 3a show the similarity of the facilities – the maximum number of ATMP types developed/produced per year for each facility is superimposed. Figures 2b and 3b show the similarity as regards question response. The proportion of total variance accounted for by each dimension is given in Figures 2a and 3a. Technically, for MCA, the map has potentially $\min\{I-1, J-Q\}$ dimensions, where I is the number of facilities, Q is the number of questions used for the analysis and J is the total number of question response categories. The only relevant dimensions in MCA are those for which the eigenvalue (principal inertia) of the indicator matrix is greater than $1/Q^{7,8}$. The total (principal) inertia is also called the total variance. The questions described below in the interpretation of the MCA contribute strongly to each dimension (aggregated contribution value $> 1/Q^{7,8}$).

Figure 2a and Figure 2b show that, for development, facilities developing the most types of ATMPs are also producing ATMPs to GMP standard (Q4) and know that they can get formal advice regarding ATMPs via the Scientific Advice Working Party (SAWP) (Q37). They are also those sites which have consulted, and are satisfied with, their national regulatory body (e.g. Paul-Ehrlich-Institute (PEI), Medicines and Healthcare products Regulatory Agency (MHRA)(Q50). Also, these facilities are regularly externally inspected against established quality standards (GMP/ European Union Tissues and Cells Directive (EUTCD)) (Q54).

Figure 3a and Figure 3b show that, for production, facilities producing the most types of ATMPs have no issues validating processes relating to ATMP manufacture (Q41) which, given the shortage of clinical material for development, is interesting. The centres producing the most types of ATMPs also communicate with their national regulatory body (Q50), and they have been producing ATMPs before the introduction of Regulation (EC) No. 1394/2007 (Q58). Substantially modified cell therapies have been defined as medicines since enactment of 2001/83/EC in each MS so many of these groups active before Regulation 1394/2007/EC was published were already manufacturing in full compliance with GMP under national authorisations.

An additional question asked if the facility had any **external** collaborations for development, production and/or quality control of cell therapies. It was apparent that collaborations were more common in facilities who are developing ATMPs as well as non-medicinal cell therapies ($p=0.015$,

result not tabulated); presumably indicating that some academic ATMP developers collaborate with external manufacturers, both academic and industrial. University/Medical School facilities which manufacture ATMP products tend to work in isolation and further collaboration/co-operation with other centres would appear to be of benefit.

Telephone Interviews

Following preliminary analysis of the questionnaires, specific questions or areas of anomaly were chosen to be explored in greater depth by telephone interviews with one or more experts in ATMP development in each MS. Twenty two interviews were conducted with centres in sixteen EU MS. The interviews were performed in English or the native language of the interviewee in a semi-structured fashion to address procedures implemented in their facility, regulatory problems encountered and general understanding of implementation of the relevant regulations in their MS. Interviewees were approached in all MS of the EU, irrespective of whether they had responded to any of the questionnaires. This can be considered (disproportional) stratified sampling.

The interviews provided the most detailed information regarding the heterogeneous implementation of the Directives and the Regulation across the EU and the impact this heterogeneity has on development:

- The definition of a cell-based medicinal product, a gene transfer medicinal product or a tissue engineered product as an ATMP, despite Regulation 1394/2007/EC, is not harmonised. Even if one requests a classification from the European Medicines Agency (EMA) it is not legally binding, and each member state may, and often does, classify the same product differently. One such example was a case of three similar products consisting of human natural killer (NK) cells expanded and activated in *ex-vivo* culture over several weeks as an anti-cancer immunotherapy. In Spain, Germany and in Switzerland these expanded products were classified as an ATMP whilst in France they were deemed “not substantially modified” and thus not regulated as a medicine. A far less manipulated NK cell product in which the cells were simply activated and not expanded was classified as an ATMP in the UK.
- All products have been taken to clinical trial successfully but the routes available for future development of these products remains very unclear. One might presume that the products regulated as medicines could follow a simple drug development pathway through increasingly complex trial and ultimately generate sufficient data for a marketing authorisation application to EMA. However, how would that be handled in France where an

identical product is able to be manufactured as a non-medicinal transplant product? Presumably the licensed NK product would have no legal protection from competition from an unlicensed alternative. This is already happening in some EU MS where academic and hospital facilities are allowed to make an autologous chondrocyte preparation in direct competition with the licensed product from Tigenix. Moreover, in the case of the NK cell product which is under clinical trial as a “non-substantially modified” preparation it is very unclear how this might be developed if the clinical trial were successful. Since it was not regulated as a medicine it cannot progress down a drug development route and is not commercially valuable. Without formal efficacy trials which are suitably controlled and powered it is hard to see how these non-medicinal products can be provided to the wider community beyond those in the initial small academic study. All correspondents confirmed that transition to GMP manufacture added significant costs but agreed that it was an essential process and that these complex therapies needed regulation. Interestingly, of those asked, none supported the concept of a lower standard of GMP for ATMPs than for conventional medicines nor was there a feeling that academic groups should be allowed to work to a lower GMP standard than industry but all interviewees shared the belief that a risk-based approach to compliance with pharmaceutical standards is required in the development of ATMPs.

- The majority of ATMPs in development are patient-directed or only able to be produced in very small batch sizes and it is unlikely that many will fit the conventional pharmaceutical model of a single batch providing treatments for thousands of patients.
- Many respondents reported favourable interactions with local regulatory authorities which operated a pragmatic approach to risk-based assessment of manufacturing procedures. Others reported extreme difficulties with obtaining approval for manufacture of specific products due to unrealistic expectations of product qualification by their individual competent authority. As an example, bone marrow derived mesenchymal stromal cells are commonly produced for therapeutic use across the EU. In some member states they are not even classified as medicines. In those where they are deemed to be ATMPs, most competent authorities accept release criteria based on sterility, four parameter immunophenotype as definition and >80% viability. However, a competent authority (CA) in a single MS has required chromosomal stability assays on all mesenchymal stromal cell (MSC) cultures which renders the trial unsustainable. Since clinical trial approvals remain within the domain of individual MS this will continue to be a problem for ATMP development and, since many are directed at orphan indications, is already hindering research which needs to be conducted

across multiple MS to reach acceptable rates of recruitment. All participants in the telephone survey said that the burden of paperwork associated with GMP, and Good Clinical Practice (GCP), compliance was a hurdle for small academic manufacturers and that open access availability of common procedures and reagent/process validations would be enormously valuable. Universities and research funding bodies do not understand the administrative challenges of GMP/GCP compliance and do not resource them. These outputs are not publishable and therefore do not contribute to academic returns against which the university is assessed by its peers. It was not felt that the regulatory burden in the EU had yet put academic clinical investigators at a disadvantage to competitors overseas although one respondent reported that patients are travelling to another EU MS to gain access to an experimental ATMP which they are unable to obtain regulatory approval to manufacture in their centre. There is widespread concern that the non-integrated approach to regulation will lead to patients travelling to other jurisdictions for novel therapies; both within and beyond the EU.

A comprehensive literature search of published papers and conference abstracts showed that the EU lags behind the US with regard to cell therapies in clinical trials; both academic and industry-led. In contrast to the EU, US GMP facilities for manufacturing for phase I/II and phase II trials are not subject to regulatory inspection and the burden of compliance is lower. The most active countries in this field outside of EU/USA are South Korea and Brazil where the burden of GMP compliance is also lighter.

Three aspects of the current regulation of ATMPs were repeatedly of concern to respondents. First, the provision of pre-clinical data for compilation of the medicinal product dossier to investigational ATMPs (IMP ATMPs) often leads to use of very contrived animal models. There is a significant risk of underestimating toxicity of human-specific biologic reagents when evaluated in animal models, even primates, as pharmacologic activity and unanticipated adverse side effects may be species-specific (9). Standard animal models may also not be predictive of toxicity due to differences in lifespan, and because the equivalent human application cannot be adequately mimicked. The testing of an “equivalent” ATMP derived from tissues from the experimental host is flawed also as the starting materials (cytokines, culture media, supplements and even culture vessels) are likely to be substantially different to the human product. This led us to conclude that the development of ATMPs requires a paradigm shift in the approach to pre-clinical testing required for clinical trial authorisation (CTA) (2, 10, 11).

The second issue requiring solution is the statutory need for a Qualified Person (QP) for the formal release of investigational medicinal products (IMPs) in the EU. In most MS the local CA approves routine pharmaceutical QPs for release of complex ATMPs. Notwithstanding the question of their competence with products considerably beyond their general field of expertise, many QPs are unwilling to accept the risks of releasing ATMPs and thus academic trialists face difficulties with regard to the release of investigational ATMPs. Training for pharmacy QPs in the manufacture of ATMPs is essential but currently lacking. In the US, there is no requirement for QP release of investigational medicines. This shortage of competent QPs also leads to a very significant added expense in ATMP manufacture which is compounded by the fact that these products usually have a very small production run with small or even single product batches. Many ATMPs are patient-specific or have a final dosing which is required immediately prior to administration. The need for QP release of each batch when a single batch treats a single patient is prohibitively expensive and may even be logistically impossible in some cases.

The third consistent and most contentious issue arising from the telephone interviews and the questionnaires was the lack of harmonisation of implementation of the Hospital Exemption Clause (HEC) in Regulation 1394/2007/EC across the MS. Several MS have not yet implemented a structure to assign HEC production licences as of the end of 2012, and in those who have done so there are wide differences in how it may be used. Most MS have applied annual limits to the numbers of a specific product type which can be manufactured under a hospital exemption clause (HEC) licence, presumably in response to the stated requirement for “non routine” production in the Regulation, whilst others apply no limits. The limit on numbers of individual ATMPs under the HEC is seen as counterproductive by over 80% of respondents. It is another potential cause of patient migration from their own MS to an adjacent MS or non-EU country to receive a treatment simply because an arbitrary maximum number of patients have been treated in a single centre in one year. Clarification of the definition of “non routine” from the Commission to the CAs in each MS is needed.

The use of the HEC for clinical trial product manufacture is forbidden in all MS as required in the Regulation. However, several CA are encouraging the use of HEC to produce ATMPs for first-in-man cases, allowing the data arising from these to be used as part of the investigational medicinal product dossier for subsequent clinical trial applications. This is in line with a recommendation by EMA CAT regarding the use of clinical data from first-in-man studies to replace pre-clinical animal studies where appropriate (11). Indeed some CA are referring to these first-in-man compassionate use cases as a new “phase 0” type of clinical study. The continued availability of the HEC for this type

of application and for the provision of ATMPs which will never be suitable for a marketing authorisation was regarded as essential by all respondents.

Discussion and Conclusion

This is the first ever survey of a representative sample of European academic GMP facilities involved in the development and production of ATMPs. Indicators of ATMP success were assessed and opinion was gathered regarding implementation of current EU legislation. Results indicated that associations *do* exist between facility characteristics/behaviour and ATMP success: development, production and communication with the authorities are unquestionably key factors for success. Experience is also inextricably linked with success – with experienced facilities in ATMP development often being those which are better staffed – these facilities “know GMP” i.e. they are comparable with (and competitive with) industry. However, it is difficult for new centres to enter the field under existing regulations and there is still a lack of facilities in academia that can take part in the field of translational research. Universities lacking these resources will fall behind in delivery and commercialisation in this field of medicine. Producing GMP-compliant ATMPs for clinical use in trials or as compassionate treatment is expensive in capital and manpower resources and it is the ongoing manpower needs which are frequently overlooked by academic centres with no history of cell therapy manufacture. The successful academic centres are predominantly those with a previous history of non-medicinal cell therapy (transplant products) provision which had pre-existing quality management systems and the staff to maintain them.

The need for QP release of investigational ATMPs presents difficulties in some MS, specifically because the batch size is often a single, patient-specific product. The lack of requirement for QP release by the FDA makes academic and industrial development of patient-specific ATMPs substantially easier in the US.

Collaboration is also important, and those facilities who manufacture ATMP products in a University/Medical School would benefit from co-operation with other centres. The need for (and lack of) quality control programmes is also important.

The inconsistencies in the implementation of the Regulation are a considerable barrier to development of ATMPs across the EU but this is largely due to the myriad differences in national drug laws which underpin the ATMP Regulation.

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References

1. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. *Official Journal of the European Union* 2007; L 324: 121-131.
2. Maciulaitis R, D'Apote L, Buchanan A, Pioppo L, Schneider CK. Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive. *Mol Ther* 2012; 20: 483-512.
3. Sethe, S; Batkai, C; Dickinson, A and Hildebrandt, M. Manufacture of advanced therapies: Academia Meets Industry. Regulatory Rapporteur. Vol 8, No 7/8, July/August 2011.
4. Barnett V. Elements of Sampling Theory. London : English Universities Press. 1974.
5. H. Abdi and D. Valentin (2007). Multiple Correspondence Analysis. In Neil Salkind (Ed.). Encyclopaedia of Measurement and Statistics. Thousand Oaks (CA.): Sage.
<http://www.utd.edu/~herve/Abdi-MCA2007-pretty.pdf>
6. M. Bendixen (2003). A Practical Guide to the Use of Correspondence Analysis in Marketing Research. Marketing Bulletin, 14, Technical Note 2. http://marketing-bulletin.massey.ac.nz/V14/MB_V14_T2_Bendixen.pdf
7. M. Greenacre (2007). Correspondence Analysis in Practice, Second Edition. London: Chapman & Hall.
8. M. Greenacre (2010). Biplots in Practice. Available free on-line.
<http://www.multivariatestatistics.org/publications.html>
9. Suntharalingam G, Perry MR, Ward S et al. Cytokine storm in a phase I trial of the anti-CD28 monoclonal antibody TGN1412. *New Eng J Med* 2006; 355:1018-1028.

10. Lowdell MW, Birchall, M, Thrasher AJ. Use of one-off, compassionate use, advanced therapy medicinal products (ATMP) as a safe and valid alternative to animal models for pre-clinical data for clinical trial submissions? Lancet 2012; 379:2341.

11. "Clinical data may, in part, compensate for non-clinical studies; inappropriate animal studies are worse than reliance upon in vitro data only". Dr Christian Schneider, Chair of EMA Committee for Advanced Therapies at ATMP Stakeholders' Workshop, EMA, London, January 2012. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/11/event_detail_000545.jsp&mid=WC0b01ac058004d5c3

Figure 1 Pie Chart showing distribution of respondents in 11 European countries (N=50)

A – Germany, B – UK, C – Spain, D – Netheralnds, E – Italy, F – Belgium, G – Austria, H – France, I – Turkey, J – Eire, K - Romania

Figure 2a Two dimensional multiple correspondence plot for ATMP development – nearby facilities reply similarly to the questions. Country identification letter is displayed alongside maximum number of ATMP types developed per year. Proportion of total variance for dimension 1=38% (eigenvalue=0.47); for dimension 2=24% (eigenvalue=0.30). Red circles indicate least successful facilities, green circles indicate most successful facilities.

Figure 2b Two dimensional multiple correspondence plot for ATMP development showing similarity between question responses. Red circles indicate question responses linked to least successful facilities, green circles indicate those linked to most successful facilities.

Figure 3a Two dimensional multiple correspondence plot for ATMP production – nearby facilities reply similarly to the questions. Country identification letter is displayed alongside maximum number of ATMP types produced per year. NA= maximum number of types of ATMP produced not available. Proportion of total variance for dimension 1=35% (eigenvalue=0.35); for dimension 2=32% (eigenvalue=0.32). Red circles indicate least successful facilities, green circles indicate most successful facilities.

Figure 3b Two dimensional multiple correspondence plot for ATMP production showing similarity between question responses. Red circles indicate question responses linked to least successful facilities, green circles indicate those linked to most successful facilities.

Table 1 Comparison of proportion of respondents in each country

Country	Percentage of facilities in sample N=50	Percentage of facilities in population N=747	<i>p</i> value ¹
A	30%	19%	0.067
B	20%	16%	0.427
C	14%	4%	0.045
D	8%	9%	1.000
E	8%	10%	1.000
F	6%	5%	0.748
G	4%	4%	0.714
H	4%	7%	0.571
I	2%	1%	0.325
J	2%	2%	0.546
K	2%	1%	0.325

¹Exact *p*-value - 2 sample proportions test

Table 2a Questions associated with ATMP development success

	<i>p</i> -value ¹
Question	
Q54 The facility regularly passes GMP/ European Union Tissues and Cells Directive (EUTCD) inspections for ATMPs produced/intended to be produced	0.015
Q37 The facility knows it can get formal advice regarding ATMPs via the Scientific Advice Working Party (SAWP)	0.02
Q4 The facility is producing ATMPs (Q4),	0.031
Q50 The facility has consulted with - and is satisfied with - a national regulatory body (e.g. Paul-Ehrlich-Institute (PEI), Medicines and Healthcare products Regulatory Agency (MHRA)	0.036
Q10 The facility is performing purifications other than immunomagnetic purifications	0.055
Q20 Increased number of technical/academic personnel involved directly in ATMP development	0.073
Q7 The facility is producing stem cell products as ATMPs (e.g. Mesenchymal stem cells)	0.074
Q58 The facility produced ATMPs before the introduction of Regulation (EC) No. 1394/2007.	0.082
Q11 The facility is performing cell manipulations (for example, expansion)	0.1

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¹Exact p -value – chi squared test

Table 2b Questions associated with ATMP production success

	<i>p</i> -value ¹
Question	
Q58 The facility produced ATMPs before the introduction of Regulation (EC) No. 1394/2007	0.022
Q10 The facility is performing purifications other than immunomagnetic purifications	0.022
Q41 The facility has no issues validating processes relating to ATMP manufacture	0.033
Q50 The facility has consulted with a national regulatory body (e.g. Paul-Ehrlich-Institute (PEI), Medicines and Healthcare products Regulatory Agency (MHRA))	0.05
Q19 The facility is developing ATMP products in a University/Medical School	0.075
Q31 The facility took part in quality control programmes for assays (e.g. National External Quality Assessment Service (NEQAS)).	0.078
Q37 The facility knows it can get formal advice regarding ATMPs via the Scientific Advice Working Party (SAWP)	0.1

¹Exact *p*-value – chi squared test