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Caught in the Gap: ATMP manufacture in Academia

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Abstract

The European regulation on Advanced Therapies (ATMPs, i.e. Cell-based medicinal products, tissue-engineered products and gene therapy medicinal products) forms part of the European project of breaking down barriers and allowing free trade and movement of products. In this, the central role of academic institutions as drivers not just of the development but also of the manufacture of ATMP is often overlooked. Many products may only reach clinical application by relying exclusively on academic facilities. Compliance with industrial standards in an inherently non-industrial environment creates particular financial, managerial and cultural pressures. At the same time, ATMP relying on a highly individualized, labour-intensive therapeutic approach challenge established concepts of regulating medicines innovation.

We briefly describe the systemic features and strategic role of academic institutions in ATMP development and conclude by charting potential partnering strategies with Industry.

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Introduction

Advanced Therapy Medicinal Products (ATMP) are medicinal products for human use, based on gene therapy, somatic cell therapy or tissue engineering. A rapidly growing area in translational research, these products represent the 'next generation' of complex medicines for complex diseases. The established model of innovation governance in medicines assumes that novel ideas and treatments are often first pioneered in Academia and later developed by Industry. Here, we will argue that this model may not apply to some ATMP and consider the regulatory strategies in Europe to address this issue. We will first consider the respective position of the public and private sector on ATMP development, then discuss some regulatory provisions that might be viewed as facilitators of academic ATMP development and finally chart ways academic ATMP development is currently being pursued.

ATMP development: Industry or Academia?

a) Applicable to Academia?

Regulation (EC) No 1394/2007 has been designed to ensure the free movement of ATMP within the European Union (EU), to facilitate their access to the EU market and to foster the competitiveness of European pharmaceutical companies in the field, while guaranteeing the highest level of health protection for patients. The Regulation amended the Medicines Directive 2001/83/EC and also established the Committee on Advanced Therapies (CAT) at the European Medicines Agency (EMA).

The scope of the regulation is „to regulate advanced therapy medicinal products which are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, in accordance with the general scope of the Community pharmaceutical legislation laid down in Title II of Directive 2001/83/EC". If an ATMP is not 'prepared industrially or manufactured by a method involving an industrial process', and not intended to be 'placed on the market' it is out of the scope of the ATMP Regulation. This has lead some practitioners to assume that the academic and hospitals sector is exempt from regulatory requirements. However, this is a misconception: The regulatory framework generally assumes that patients can only be treated with either Medicinal Products or Investigational Medicinal Products – to which largely the same manufacturing requirements apply.

b) Industry engagement in ATMP

It has been observed that for many ATMP products, especially cell-based and patient-specific treatments, the pharmaceutical industry has limited interest in playing its 'usual' role of financing development and of acting as a sponsor in clinical trials.

Several reasons can be suggested. We can differentiate between at least three 'economic' and three 'cultural' reasons:

Economic

1) **Intellectual Property**. Since ATMP are often not based on a 'simple' cause-effect model, the intellectual property landscape is often more complicated with these products, making it difficult to ringfence intellectual property, establish freedom to operate and anticipate the effects of competition.
2) **Orphan.** Many current ATMP, especially in gene therapy are applicable for rare or orphan indications. While it is now established that orphan drug status in itself is no bar to profitability, the challenge with developing and finding politically acceptable reimbursement for such products remain (1).
3) **Scaleability.** Even if ATMP are potentially applicable to a large patient population, their cost and complexity often render it impossible to conduct trials on a large patient population – which is traditionally the specialist expertise that industry brings to the table in translational research. The high cost effort per treatment also yields uncertainties about effective reimbursement (2).

Cultural

1) **Complexity.** Many ATMP are manufactured differently from mainstream medicines, requiring investment into new expertise. Cell therapy products often do not have a clearly defined mechanism of action, gene therapy presents unique challenges of long-term systemic effects, and tissue engineering targets a complex interface of material science and biology. The selection, enrichment or genetic modification of cells and tissues often enhances their sensitivity the effect of which cannot be replicated *in vitro*.
2) **Surgical.** Many ATMP are seen to be more closely related to transplantation, an area that does not interface much with established industrial R&D.
3) **Transferability.** Many ATMP require very specialized, tacit clinical expertise that cannot easily be transferred. Cell populations are necessarily heterogeneous and dynamic and purification protocols as they are applied in 'established' biotechnology may actually prove detrimental to the efficacy of the final product.

We do not mean to suggest that ATMP are not attractive for industrial development. Other factors play a role (3) and in fact, the industry sector using ATMP is increasing markedly (4). However, the above considerations suggest that there are a number of factors that may militate against ATMP development in the private sector and complicate technology transfer from the public sector.

c) Academic engagement with ATMP

It follows from the above that academic facilities are an important source for the development of ATMPs. Not only do they participate in the translation of pre-clinical academic research into GMP, but some products may only reach clinical application by relying exclusively on academic facilities. A number of 'hidden' ATMP have been manufactured for clinical and development use without marketing authorisation (5). Although these parameters are changing, financing for tissue engineering (6) and cell therapy (7) has been largely based on public sector funding.

Regulatory 'assistance' for academic ATMP development?

Given the particular role of Academia and hospitals in ATMP development, are there any legal provisions that facilitate their contribution?

a) Fee reduction

Specific incentives for small and medium sized enterprises (SME) exist in the ATMP area. (SME are defined as per Commission Recommendation 2003/361/EC4: staff headcount <250 and balance sheet total ≤ € 43 million). In recognition of the particular scientific novelty raised with many ATMP, all parties receive a 65% fee reduction on scientific advice from the EMA. SME (and not Academia) are eligible for a 90% fee reduction. (The fee payable for a marketing authorisation and fees charged by the EMA for post authorisation activities during the first year thereafter are reduced by 50%, if the applicant is an SME or a hospital and can prove that there is a particular public health interest in the Community in the ATMP – but this applies only during the transitional period ending Dec.30th 2011.)

b) The 'Certification'

A new certification system aims at giving SMEs an incentive to develop ATMPs. Under this scheme, the Regulator can 'certify' data as being of sufficiently high quality for regulatory consideration. It is expected that innovators will then be able to raise capital for further R&D. The scope of the evaluation is to certify that each submitted study complies with the relevant scientific and technical requirement set out in the Annex I to

Directive 2001/83/EC and adequately follows state-of-the-art scientific standards and guidelines. The relevant provisions have been laid out in Commission Regulation (EC) No 668/2009 in which Article 2 1(e) and (f) define the minimum quality and non-clinical data in the certification application. EMA is further tasked with preparing the scientific guidelines (Art 5). The certification procedure is independent from a future marketing application, but may facilitate the evaluation of any future applications based on the same data. The certification procedure covers only a scientific evaluation of experimental data (quality/non-clinical) already generated. Whether such a certification scheme will prove a worthwhile investment for innovators remains to be seen. Astonishingly though, this mechanism is not accessible for Academia.

c) The 'Hospitals Exemption'

Under Article 3 (7) of 2001/83/EC, there is an exemption from central authorisation for ATMPs which are prepared on a non-routine basis and used within the same Member State in a hospital in accordance with a medical prescription for an individual patient. Member States are requested to lay down rules for authorising these products by the national Competent Authority whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined. (While searching for 'exemptions' to the process of marketing authorisation Art.5.1 of the Medicines Directive also applies to ATMP and may well be the preferable route).

It is correct to assert that this "exemption was included in the Regulation in recognition of the small scale and developmental nature of activity carried out in some hospitals, which argued for a degree of flexibility over the nature of regulatory requirements" (8). However, it is uncertain how much the exemption can actually be relied on for 'development'. Whether this provision is useful and applicable will depend not only on the circumstances of the individual case but also on the extent to which the Member State has recognised and interpreted the provision. Similar to 'compassionate use' cases (9), there appears to be considerable heterogeneity in the approach to these cases across Europe.

Academic ATMP Landscape

What are the constituent features of the Academic ATMP Landscape?

a) Academic GMP Facilities

Given that, for reasons outlined above, the manufacturing burden shifts to Academia in ATMP, the sector has needed to develop new infrastructures to cope with this demand: Substantial investment has been earmarked to bring university and hospital facilities to

the required level. Many approaches have been taken in building, financing and maintaining academic GMP facilities: some facilities are entirely university-based, others are funded by external resources. Some function in combination with non-profit partners, others have been build with public funds and then been leased to Industry.

A growth in Academic GMP facilities has been observed in some Member States (10), however, a conceptual view on how many facilities may be needed is lacking, and it is unknown what formula should be used to define the optimal number, size and degree of organization.

In the transition to licensed medical products, the huge financial investments needed for the compliance with 'industrial' standards remain with the academic institutions. Academic GMP facilities are requested to comply with industrial manufacturing standards in an inherently non-industrial environment. GMP knowledge is sparse in Academia; it has traditionally resided in pharmacy and recently grown in transfusion medicine as this field became more regulated.

b) Academic cooperation

A higher probability of success may lie with broader network structures involving academic institutions, industry and national authorities interacting in a consolidated manner, and in joint efforts to promote translational research in the EU. In 2002, the European Strategy Forum on Research Infrastructure (ESFRI), which represents the Member States' research ministries and the European Commission, endorsed large research infrastructures for this purpose (11). The European Advanced Translational Research Infrastructure in Medicine (EATRIS), with translational centres to be established for research from „bench to bedside" and also a flow of information from „bedside to bench", is currently approaching its implementation phase, and is planning to be operational in 2015 (12). This highlights the timeline and the financial and logistic effort needed, clearly beyond the capacities of purely academic network structures. Smaller networks focus on an assessment of existing academic GMP facilities in Europe, and on their perception of Regulation 1394/2007/EC and the consequences on Academia (13). There are also a number of collaborative national and regional networks and a thematic 'ATMP arm' in scientific societies such as in the Joint Accreditation Committee by the European Group for Blood and Marrow Transplantation (EBMT) and the International Society for Cellular Therapy (ISCT). These efforts may help to establish platform for consolidation, networking and sharing of best practice.

Some European research institutions have begun to network available GMP facilities at an EU level. The idea is to promote academic-led "first-in-man" gene therapy trials by linking the available expertise, GMP production facilities and human skills, with the aim of providing a proof of efficacyfor a range of technologies. At this point, the technology could be transferred to the private sector which would then take over further development taking advantage of academic knowledge and know-how (14). However, the extent of this effort is underestimated, and the capacities in Academia to handle this must be put into question.

c) Partnering Strategies

Ultimately, it seems improbable that ATMP development can be conducted in the academic sector exclusively. Instead, new partnering frameworks could emerge that rely on the instruments mentioned above, and play to the respective strengths of the partners. Some of the 'old models' will need adjusting: While traditionally Industry brought regulatory compliance expertise to medicines development, it currently seems that industry partners from a biopharmaceuticals perspective tend to introduce unwarranted delays by lacking the appreciation that some ATMP will remain heterogeneous (whereas this appreciation is affirmed by regulators, at least in rhetoric). The delay of some clinical trials has been attributed to the outsourcing of manufacture to independent companies.

A proportionate regulatory framework will by necessity involve the voices and perspectives of patients (15), and the academic and hospital sector are arguably better positioned than Industry to establish such dialogues and partnerships. As long as the public collaborators manage to hold on to their identity as representatives of a broader stakeholder community, such relationships present an opportunity for more involvement, feedback, and transparency. Partnering strategies may also involve a more localised approach to therapy delivery, focussing on centres of excellence rather than global generic rollout. The last two decades have seen a marked increase in the assertiveness of academic bodies as commercial protagonists – in stark extrapolation of developments observed in biotech, it seems likely that if the Academy fails to find commercial partners it may simply create them as dependent satellites.

Conclusions

It has been suggested that the regulatory regime for ATMP overall is inappropriate and potentially damaging to innovation (16,17), on the other hand it can be argued that the reasons Industry is reluctant to get involved in ATMP rest not with the regulatory regime, but with the scientific evidence base (18). Certainly, tentative evidence

regarding the promise of some ATMP is not lacking. The number of small-scale exploratory studies using cell and gene therapy approaches is by now very considerable. What we fail to see is the widespread attempt towards 'proper' validation through larger scale trials. It may be that this aspiration is unwarranted: perhaps the most effective transition out of the 'gap' is by avoiding the well travelled road of escalating phases of clinical trials with escalating costs and a growing Industry involvement. Instead, local practice under 'hospitals exemption' or protracted trials may present an alternative to seeking the holy grail of marketing authorisation. This does not mean that such regimes need be unprofitable or closed to Industry participation. However, successful business models will need to integrate the academic and hospitals roots of the product in the value creation.

Authors

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References

1. Denis A, Mergaert L, Fostier C, Cleemput, I, Simoens S. Issues surrounding orphan disease and orphan drug policies in Europe. Applied Health Economics and Health Policy, 8(5), pp 343-350, 2010

2. Ginty PJ, Rayment EA, Hourd P, Williams DJ. Regenerative medicine, resource and regulation: Lessons learned from the remedi project, Regenerative Medicine, 6(2), pp 241-253, 2011

3. Plagnol AC, Rowley E, Martin P, Livesey F, Industry perceptions of barriers to commercialization of regenerative medicine products in the UK, Regenerative Medicine, 4(4), pp 549-559, 2009

4. Lysaght MJ, Jaklenec A, Deweerd E, Great expectations: Private sector activity in tissue engineering, regenerative medicine, and stem cell therapeutics, Tissue Engineering - Part A, 14(2), pp305-315, 2008

5. Mason C, Manzotti E, Regenerative medicine cell therapies: numbers of units manufactured and patients treated between 1988 and 2010, Regenerative Medicine, 5(3), pp 307-313, 2010

.6 Michael JL, Reyes J. The Growth of Tissue Engineering. Tissue Engineering. 2001; 7(5): 485-493.

7. McKernan R, McNeish J, Smith D, Pharma's developing interest in stem cells, Cell Stem Cell, 6(6), pp 517-520, 2010

8. UK Department of Health "Explanatory memorandum to the Medicines for Human Use (Advanced Therapy and Miscellaneous Amendments) Regulations 2010" Ref. 2010 No. 1882 http://www.legislation.gov.uk/uksi/2010/1882/pdfs/uksiem_20101882_en.pdf

9. Whitfield K, Huemer KH, Winter D, Thirstrup S, Libersa C, Barraud B, Kubiak C, Stankovski L, Grählert X, Dreier G, Geismann S, Kuchinke W, Strenge-Hesse A, Temesvari Z, Blasko G, Kardos G, O'Brien T, Cooney M, Gaynor S, Schieppati A, Serrano M, de Andres F, Sanz N, Hernández R, Kreis G, Asker-Hagelberg C, Johansson H, Asghar A, Husson JM, Demotes J, Gluud C, Compassionate use of interventions: results of a European Clinical Research Infrastructures Network (ECRIN) survey of ten European countries, Trials, 11:104, 2010

10. Williams RK, Osborne A, Small Scale Biomanufacturing – The UK Experience, European Biopharmaceutical Review, pp 76-79, 2009

11. cf.: http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri

12. cf.: http://www.eatris.eu/EATRIS/PreparatoryPhase.aspx

13. cf.: http://www.academic-gmp.eu

14. Cohen-Haguenauer O, Creff N, Cruz P, Tunc C, Aïuti A, Baum C, Bosch F, Blomberg P, Cichutek K, Collins M, Danos O, Dehaut F, Federspiel M, Galun E, Garritsen H, Hauser H, Hildebrandt M, Klatzmann D, Merten OW, Montini E, O'Brien T, Panet A, Rasooly L, Scherman D, Schmidt M, Schweitzer M, Tiberghien P, Vandendriessche T, Ziehr H, Ylä-Herttuala S, von Kalle C, Gahrton G, Carrondo M. Relevance of an academic GMP Pan-European vector infra-structure (PEVI), Curr Gene Ther, 10(6), pp 414-22, 2010

15. Kent A, King NMP, Cohen-Haguenauer O, Toward a proportionate regulatory framework for gene transfer: A patient group-led initiative, Human Gene Therapy, 22(2), pp 126-134, 2011

16. Sethe S, The implications of "advanced therapies" regulation, Rejuvenation Res, 13(2-3), pp 327-8, 2010

17. Tiedemann G, Sethe S. Regulatory frameworks for cell and tissue based therapies in Europe and the USA. In: Steinhoff, G (Ed): Regenerative Medicine – from Protocol to Patient, Springer 2011, p 946

18. Bravery CA, Regulating interface science healthcare products: myths and uncertainties, J R Soc Interface, 2010;7 Suppl 6, pp S789-95, 2010