Manufacture of advanced therapies: Academia meets industry

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Introduction

Funded by the European Framework Programme, 'Academic GMP' is a research project aimed at generating new knowledge on the impact of ATMP-focused regulations. The consortium's initiatives include comparing the experiences of various stakeholders, conducting a European survey of non-industry facilities in this sector, analysing publications and innovation statistics in relation to advanced therapies and considering regulations and guidance from the perspective of better regulation principles. The workshop, organised by Academic GMP and held in March 2011, is one of a series of events planned to meet the consortium's aims. Around 40 selected delegates attended from across Europe, including representatives from regulatory authorities, small and medium-sized enterprises (SMEs), industry, clinicians, GMP staff and experts in regulation, law and innovation management.

Background

Rules on pharmaceutical good manufacturing practice (GMP) have evolved over decades to ensure standards of quality, safety and efficacy in the development of pharmaceutical products. They stipulate a 'clean room culture' where every step is carefully monitored, controlled, validated and recorded. It is universally acknowledged that established GMP standards cannot simply be imposed on advanced therapy medicinal products (ATMPs) without modification, for reasons outlined in this article. It is not yet clear to what extent the regulations have managed to adequately address the *sui generis* nature of ATMPs.

Although Directive 2001/83/EC is oriented towards the granting of a marketing authorisation, its reach does not just extend to the launching of a finished product onto the market. Stipulations for GMP apply to every stage of development in clinical trials and even reach into nonclinical development. Thus, GMP-related regulations and guidelines shape the innovation trajectory of ATMPs in major ways. During clinical trials, these rules require in-depth discussions between manufacturers and regulators. Traditionally, only large pharmaceutical companies are equipped to shoulder the burden of maintaining GMP manufacturing facilities, of coordinating complex trials to the requisite standard and to meet the considerable bureaucratic requirements. However, it has been observed that for many ATMPs, 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 have been suggested, including:

- Many ATMPs are manufactured very differently from mainstream medicines
- The intellectual property rights (IPR) landscape is often more complicated
- It is often not possible to conduct trials on a large patient population
- Many ATMPs require very specialised, tacit clinical expertise that cannot easily be transferred
- Many ATMPs are seen to be more closely related to transplantation, an area that does not interface much with industrial R&D.

In many instances, the spin-out of ATMP development from the academic GMP facilities to industrial partners also meets technical difficulties: production of a specific ATMP requires a highly specialised skill mix, with elements of scientific expertise, technical know-how and a strong clinical link to the treatment protocols of the individual patients. Consequently, academic facilities are major contributors to the development of ATMPs. Not only do they have an important function in the translation of nonclinical academic research into GMP, but some products may only reach clinical application by relying exclusively on academic facilities.

Thus the development of advanced therapeutics emerges to a considerable extent from academic institutions. Substantial investment has been earmarked in the public sector across Europe to bring university and hospital facilities to the required level. However, in assuming this role, academic GMP facilities face particular challenges.

Workshop presentations

Although not a focus of the workshop, brief presentations highlighted different perspectives from within and on the academic GMP landscape.

Martin Hildebrand, Director at the Hannover Medical School IFB-Tx, GMP Development Unit, offered a perspective on the Academic GMP landscape. He explained that some facilities are truly 'universitarian', some are funded by external resources, some function in combination with non-profit partners, and some have been spun out and later reintegrated. Some facilities work on an open-access basis, others only do R&D and do not contribute to clinical treatments. Conflicts have arisen between pharmacists, transfusion medicine specialists and haematologists where the GMP facilities are caught between different manufacturing and processing expectations.

Mark Lowdell, **Director of Cellular Therapy at University College (UCL) London,** shared two examples of interaction between academia and industry. In a collaboration between UCL and a UK SME on a Phase I/II trial, company staff received GMP training at UCL, where the SME was also renting space and relying on a UCL Qualified Person. This allowed for rapid progress, with Phase III multicentre trials commencing within six months of starting in the laboratory at UCL. This was in contrast to a more problematic collaboration with a US company which only aimed to purchase the intellectual property and to outsource production at US biomanufacturing facilities. As those facilities do not have ATMP experience and struggle with challenges regarding standardisation and product heterogeneity, this project has lingered in the starting phase.

Karin Hoogendorn, Centocor Ortho Biotech (a member of the Johnson & Johnson conglomerate) US, offered a 'Big Pharma' perspective, telling delegates that many large pharmaceutical companies welcome the regulation as flexible and appropriate. In her opinion, the bottleneck does not lie in the regulation but in its science. Product characterisation, comparability, testing and traceability are seen as major hurdles to product development.

Marc Barthold, **Miltenyi Biotec, headquartered in Cologne, Germany,** conveyed the perspective of a different type of industry collaborator: a supplier of tools and reagents. Miltenyi Biotec interacts with academia in clinical development as suppliers of clinical grade material for clinical research and as GCP support. From a supplier perspective, it may be helpful if regulations were more specific regarding specifications to develop a product portfolio. Generally, the ATMP legislation is seen as helpful simply by virtue of its existence.

Dmitry Polyntsev, **President, Alkor Bio, based in St Petersburg, Russia,** represented the perspective of an SME from outside the EU. He perceived that ATMP manufacturing is currently on hold in Russia due to uncertainties regarding stem cell regulation. In attempts to make a choice on which regulatory provisions to adopt for manufacture, the same dilemmas as in the EU were observed – adoption of regulatory standards developed for 'established' medicines was seen as inappropriate for cell therapy.

Christopher Bravery, Director, Advanced Biologicals, UK, challenged some of the principles of the workshop as outlined above. He suggested that GMP controls on somatic cell therapy were already required before the ATMP regulation came into being. Arguably, Directive 2004/23/EC and previously 2001/20/EC had a much greater impact on 'academic GMP' in this sector. He did agree, however, that there was often a 'culture clash' when academics faced regulation and product development.

Lucy Foley, Research Associate in BioBusiness, University of Newcastle, UK, discussed the UK ATMP Manufacturing Community which she helped to establish. This community, with a database of facilities, joint meetings and a collective voice might be seen as an initiative to be emulated in other countries, or even at a European level.

Following the above presentations, breakout discussions were held where participants tackled questions regarding experience and policy.

Characterising the role of academia in ATMP development

As many ATMPs target a small patient population, there may be insufficient commercial scale for industry. However, since orphan products function commercially, it was argued that many ATMPs could also use orphan drug mechanisms for development and marketing. The main delineating feature may not be market size, but complexity of product and manufacture.

The 'cultural' difference is often described as one of 'different languages'. It was suggested that academia is sometimes not considered as a serious partner by industry, and conversely industry lacks appreciation of the intensely clinical framework within which ATMPs are developed and administered. This situation is characterised by one or more of the following parameters:

- A product that is not amenable to 'off the shelf' mass production
- High complexity leading to high cost production with uncertain profit margins
- Highly personalised (patient-specific) treatment modality
- High degree of scientific uncertainty regarding which factors are significant in ascertaining product efficacy and safety
- High degree of product variability
- High level of individual skill and tacit knowledge.

In short, the innovation profile of certain ATMPs is comparable to experimental transplantation medicine. As with transplantation products, it can be argued that the ATMP manufacturing process is an integral part of development and that any manufacturing practices elude standardisation and transferability. Complexity and lack of commercial incentives mean that any perceived barriers to development may stifle innovation in this segment. The argument for different, less prescriptive regulatory controls on manufacturing in these scenarios is thus based on three grounds:

1. Existing rules and experiences are inappropriate
2. Risk management is conducted differently in this sector, with more hands-on monitoring of individualised risks
3. The final procedure will likely not be scalable; there will be limited desire to achieve European-wide marketing authorisation.

A situation where academic researchers are daunted or confused by the regulatory requirements would not only be to the detriment of European competitiveness in ATMPs, but also delay clinical and other applied translational research.

What aspects of the ATMP regulation could be changed or improved?

In a discussion relating to desired amendments to the regulation, the topics of education, better networking and consolidation of standards were all mentioned as potentially beneficial. However, participants agreed that there remains a territory in ATMP development where industry would be reluctant to tread and expectations on GMP manufacturing would stifle the development of new cures by public sector protagonists.

Workshop participants considered the so-called 'hospital exemption' (Art.3-7 of Directive 2001/83/EC as amended) as a potential tool for academic or hospital-based innovation to transcend this situation. The scope of the ATMP regulation is limited to products which are intended to be placed on the market in EU member states and which are either prepared industrially or manufactured by a method involving an industrial process. Delegates remarked that the way the hospital exemption is interpreted and used apparently differs greatly in different member states. However, the exemption is expressly not a tool to avoid GMP requirements in clinical trials. It was mooted that exemption could be used to gain initial 'first in man' experience with certain ATMPs before launching into fully-fledged clinical trials, but this construction leaves a lot to be desired in terms of charting clear and robust innovation pathways.

Consequently, participants agreed that the following question was worthy of further investigation:

"Would it be possible to establish a framework within which to permit 'small scale' clinical experimentation and development of ATMPs with a view to establishing the procedure as a local therapy without requiring a fully developed set of GMP controls?"

Participants agreed to pursue this question, among others, in subsequent research by the consortium.