Institutional Profile

The ATMP Manufacturing Community (amc)

This article describes the emergence, during 2011, of a community of best practice for the GMP manufacture of cellular therapies in the UK. The community originated in response to the anticipated demand for manufacturing capability as the UK increases its throughput of successful cell therapies. The community will catalyze the development of robust manufacturing processes essential to establishing the cell therapy industry in the UK. The Advanced Therapy Medicinal Product (ATMP) Manufacturing Community (amc) was formed in September 2010 as a community of best practice for cell therapy manufacturing in the UK. During 2011, the amc held three technical meetings, established an online presence via a website, Twitter and LinkedIn and now has 191 members. The amc aims to share nonconfidential information, develop best practice, inform and influence. The amc is also well placed to showcase UK GMP cell therapy manufacturing capability, which is currently well distributed and mostly focused on small-scale manufacture for clinical trials. The amc welcomes and encourages anyone with an interest in cell therapy manufacture to join.

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A successful cell therapy industry is extremely important to the UK economy because it offers significant benefits to patients and to the National Health Service and because it provides an opportunity to grow a knowledge-based industry that can remain largely local. There are currently 26 cell therapy companies in the UK. If the global cell therapy market is to grow as predicted by Mason *et al.* [1], then it will be worth US\$5.1 billion by 2014. Additionally, there is great potential for the provision of related services such as raw materials supply, manufacturing equipment, quality control and logistics.

Cell therapy scientific research and development in the UK is world leading [101], with notable achievements beginning as early as 1978 with the world's first 'test tube baby' [2], and more recent successes such as the Macchiarini trachea [3], limbal stem cell transplantation [4] and stem cells for heart failure [5]. Scientists in the UK are developing stem cell therapies to treat diseases of all prevalences, ranging from orphan diseases such as epidermolysis bullosa [6], to those that affect much

larger proportions of the population, such as age-related macular degeneration [7].

Aside from blood and bone marrow processing, cell therapy manufacture is still in its infancy. Currently, the processes used to produce cells for preclinical and early-stage clinical studies are more suited to the bench than they are to full-scale manufacture. There is a translational gap between science (research and development) and implementation (routine manufacture) that requires a bioprocess-engineering approach which is often ignored by those developing early-stage cell therapy products.

In the UK, there is a strong cell therapy community, and frustrations about this translational gap were routinely voiced at a number of collaborative events (e.g., Newcastle Biomedicine Sandpit, RegeNer8, Clinical Needs Workshop, London Regenerative Medicine Network [LRMN] and related Technology Strategy Board projects). Organically, the need for a working group to address these needs emerged, and in September 2010 the Advanced Therapy Medicinal Product (ATMP) Manufacturing Community amc

was formed. The amc was set up to catalyze the development of robust manufacturing processes essential to establishing the cell therapy industry in the UK. The amc aims to build a critical mass that will:

- Share noncommercial information so that members can learn from the experience of others;
- Develop best practice to reduce the barriers to cell therapy manufacture;
- Inform and influence regulators and suppliers and help to drive down cost and risk;
- Showcase UK GMP capacity to make it easy for developers (national and international) to find a facility that best meets their demands.

The amc

The amc, now with 191 members, has come some way to building a representative body for UK cell therapy manufacture. The amc has appointed an eminent advisory board (see TABLE 1) and has developed an online presence through its website [102], LinkedIn (ATMP manufacturing community) and Twitter (@ATMP manufacture).

The amc hosts regular technical meetings. Four successful meetings have already taken place: the first (February 2011 at University College London, UK) was focused on cell therapies currently in manufacture, the second (July 2011 at the National Institute for Biological Standards and Control, UK) was focused on regulatory aspects, the third (September 2011 at Newcastle University, UK) was focused on troubleshooting (with suppliers)

technologies for cell therapy manufacture and the fourth meeting (in February 2012) was held at Kings College Hospital, UK and focused on release testing and analytical tools. Each of the meetings was well attended by community members. The meeting format is very interactive, enabling community members to learn from each other, troubleshoot each other's GMP manufacturing issues and inform suppliers and regulators of their knowledge-based opinions. Additionally, each technical meeting includes an overview of a UK GMP facility. The amc has good links with HealthTech and Medicines Knowledge Transfer Network; the second technical meeting at NIBSC was cohosted with their Bioprocessing for Advanced Therapies special interest group.

Recognizing the grass roots nature of the community, the amc currently has no separate legal identity or budget and a flat and consensual organization structure. The administrative work is carried out by a working party consisting of Angela Osborne (eXmoor pharma, UK), Lucy Foley (Newcastle University, UK) and Emily Culme-Seymour (LRMN). The advisory board (TABLE 1) meets biannually to support and direct the amc. Community members are encouraged to input, sponsor and shape future events. In order to become more inclusive and representative of cell therapy manufacturing, it is intended that future events will involve related communities both within and outside of the UK.

The amc has an active LinkedIn group where members of the community can discuss new regulations, ask for advice and keep up to date with cell therapy

Table 1. The Advanced Therapy Medicinal Product Manufacturing Community advisory board.

Name	Association
Aidan Courtney	Roslin Cells
Farzin Farzaneh	Kings College London
Paul Kemp	Intercytex
Mark Lowdell	University College London
Chris Mason	University College London
Angela Scott	Angel Biotech
Daniel Smith	HealthTech and Medicines Knowledge Transfer Network
Glyn Stacey	UK Stem Cell Bank
Michael Whitaker	Newcastle University
David Williams	University of Loughborough

manufacture. It also maintains an up-to-date Twitter profile. The amc web presence [102] was set up in June 2011 and will continue to grow and become more interactive. In the coming months, it will showcase the UK GMP ATMP manufacturing facilities, as well as adding a supplier section, a dedicated forum and a portal for sharing best practice documentation.

So far, the amc has been well received and feedback from community members has been very positive, for example:

“I believe the amc has already been very valuable as it is providing links between scientists and GMP production experts which can only benefit the rate at which basic research can be translated to the clinic. In addition I think the community will be increasingly important as an organization that can apply pressure to vendors, in order to provide this rapidly growing area with the equipment and reagents it needs to succeed in a GMP manufacturing environment.” Katy Newton, Manager (Immunotherapy products and services), Cell Medica, UK.

“...there is a need for constant review and reflection in this rapidly developing field. Alongside this is the requirement to rapidly inform newcomers as well as the establishment. amc strikes a balance between these, providing a forum for likeminded individuals to meet and discuss matters in an informal environment where the opportunity to digress from the specifics of the topic in question leads to healthy and sometimes quite lively debate. The structure of the meetings is conducive to this, being built around formal presentations and informal network sessions that are inclusive, with members ranging from fresh faced young postgraduates to wizened professionals, all coming from a base that includes both public and private sector, science and non-science.” Peter Bishai, Deputy Research Facilities Manager, King’s College London School of Medicine, UK.

The amc has also gained great interest from suppliers who wish to use the community as a knowledge resource as they develop new technologies and products. The amc’s effort to promote UK GMP manufacturing facilities has resulted in requests on facility availability from cell therapy companies both within and outside of the UK.

UK GMP ATMP capacity

The amc assessed the UK capacity for the GMP manufacture of cell therapies in part to identify potential members and in part to provide a ‘shop window’ for UK facilities. Additionally, knowing the current UK offering in GMP ATMP manufacture would enable the industry to make an informed judgement as to when additional capacity would be required.

A questionnaire was distributed to all known facilities. The list of facilities was generated via word of mouth, web searches and the list of Human Tissue Authority licenses available online. The questionnaire included facility contact information, facility size, grade, types of therapies manufactured and facility availability/utilization, as well as any licenses held. In addition, the questionnaire described the potential establishment of the amc and asked whether this type of community would be valued.

Figure 1. Licensed clean rooms across the UK.

P: Planned.

Between December 2010 and January 2011, 66 questionnaires were issued; 26 facilities responded and the outstanding units were mainly bone marrow-processing centers. Three facilities have since updated their license status. **FIGURE 1** shows license distribution across the UK. Notable is the increase in Medicines and Healthcare products Regulatory Agency (MHRA) Manufacturer's Authorisations for Investigational Medical Products, which is a direct result of the change in regulations [8] that has meant that more cell therapies in development will need to be manufactured under an MHRA license. Currently, the UK has 12 MHRA-licensed facilities for ATMP manufacture and a further eight are planned. This represents 82 separate processing suites (47 with an MHRA license and 27 with licenses planned).

In order to understand the spread of therapy types across the facilities, rudimentary questions were asked about current/recent products manufactured. The responses are summarized in **FIGURE 2**. In addition, our primary question was whether or not a community such as the amc would be valued, and the response was a unanimous 'yes'.

A total of 20 of the 26 facilities that responded have given permission for their facility details to be published, and these will be available shortly on the amc website [102]. Of the 26, 19 have reported that their facilities are not fully utilized, and of

these, 12 facilities are available for third-party use. There are currently 41 individual suites with an MHRA license (and an additional eight planned) potentially available for third-party use and currently not fully utilized.

Currently, it would appear that there is adequate capacity of MHRA-licensed clean rooms for ATMP manufacture in the UK. Predicting future demand is difficult because of uncertainty regarding how many cell therapy clinical trials will be carried out in the UK and exactly when. In addition, each trial is hugely variable in terms of manufacturing volumes, types of processes and resources required. It is, however, possible to draw some general conclusions:

- The cellular therapy market is growing [1] and the number of trials is likely to grow correspondingly. This will lead to the need for more manufacturing facilities;
- As the trials move on from Phase I, the manufacturing throughputs will increase and there will be a need to move away from the currently available grade A/B clean rooms and into grade D rooms with closed processing;
- For all trials, there is a need to have technology transfer space to enable process development and process improvement. This pilot plant space needs to be GMP-like, but not necessarily licensed, and is in short supply. This pilot plant space will also be required by equipment manufacturers as they develop new technologies;
- GMP manufacturing space costs a lot to install, operate and maintain (even when empty). It can also take several years to plan, install, qualify and get licensed.

The current UK model of having many disparate and relatively small licensed manufacturing facilities matches the current need. As demand increases, it makes sense to provide a matching service such that existing capacity is better utilized, and this will be provided by the amc. Longer term, there is a need for facilities with larger capacity grade D clean rooms, additional pilot plant capacity and associated supporting infrastructure.

Figure 2. Expertise in facilities that responded to the questionnaire.

HESC: Human embryonic stem cell.

The amc welcomes and encourages anyone with an interest in cell therapy manufacture to join at [102].

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Highlights

- Translating the strong scientific base in cell therapies in the UK is essential. The UK's centralized health system is well placed to encourage and support clinical trials for cellular therapies and their subsequent widespread adoption. In addition, the UK cell therapy industry can take advantage of existing biopharmaceutical experience that is transferable to this new therapeutic class.
- Routine GMP will increasingly become the bottleneck as more therapies emerge from research and development. At present global capability in this area is in its infancy and the UK can gain competitive advantage by consolidating and sharing knowledge and experience across its disparate manufacturing sites.
- Establishing the Advanced Therapy Medicinal Product Manufacturing Community has shown that there is a real interest in growing this capability in the UK. The Advanced Therapy Medicinal Product Manufacturing Community has been formed organically by individuals concerned with the challenges of day-to-day GMP of cellular therapies.
- As witnessed historically in the biopharmaceutical industry, the challenges facing routine manufacture of cell therapies are different from those facing research and development and therefore, finding solutions will require different skills. Currently, small-scale GMP is carried out using similar processes and equipment to that used in research and development and often by research and development personnel. As manufacturing volumes increase there will be a need to increase process efficiency and drive costs down; this will require significant process and analytical development, new processing techniques and improved traceability. Bioprocess engineering has a key role to play here.

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