

National Measurement System



Keeping cells under control

The critical role of standardisation in supporting innovation in regenerative medicine

Standardisation is essential for ensuring the comparability and reliability of the measurements supporting all aspects of medical treatment. This is particularly important in rapidly developing areas based on new technologies, such as regenerative medicine.

LGC has played a key role in developing the underpinning metrology which supports testing strategies in the regenerative medicine area both through the development of measurement methodologies required to characterise products, and through the production of documentary standards. This case study focuses on these documentary standards and their impact in this exciting healthcare area.



*Setting standards
in analytical science*

1. Introduction

Regenerative medicine is a branch of science that develops products which can "replace or regenerate human cells, tissues or organs in order to restore or establish normal function".¹ This includes the transplantation of cells (cell therapies) to treat damaged tissues or to secrete factors to restore homeostasis, e.g. the transplantation of pancreatic islet cells into the liver to secrete insulin for the treatment of diabetes or the transplantation of neuronal cells into the brain to treat patients following a stroke. Regenerative medicine also includes tissue engineering where cells are combined with bio-materials to grow organs outside of the body in preparation for transplantation, e.g. using stem cells combined with biodegradable polymers (Figure 1) to grow a replacement bladder or combining fibroblast and keratinocyte cells with collagen to engineer skin.

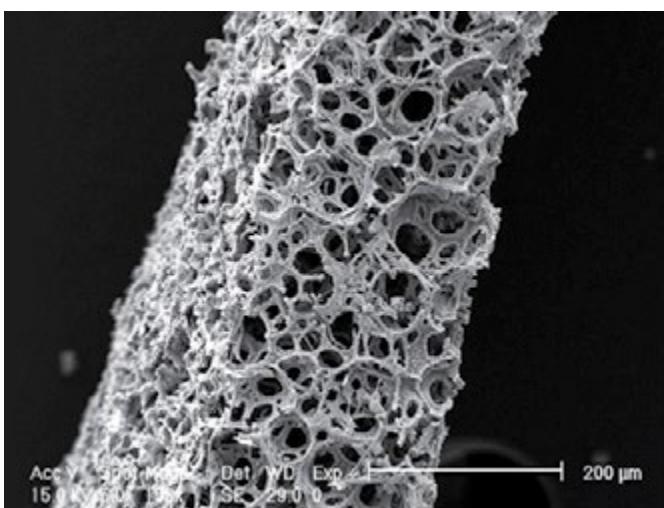


Figure 1. Example of 3D scaffolding used to provide a tissue-like environment for cells to grow. (Courtesy of Reinnervate, www.reinnervate.com)

As healthcare provision has improved over the past few decades there has been a demographic shift towards an ageing population. This has led to increased numbers of elderly people who are living longer and, as a consequence, require increased healthcare provision with associated costs. According to the European statistics database (Eurostat) the population in the EU in 2011 stood at 501 million,² with 16% of the population over the age of 65 (~80 million). The percentage of over 65s is projected to rise to 22.6% by the year 2030,³ a significant increase for this age group. With this change in demographics, the healthcare markets for indications common among older populations will undoubtedly grow. These include heart disease, cancer, stroke, pulmonary disease, diabetes and osteoporosis. This could have a particularly large economic impact for the NHS where up to 80% of healthcare costs are presently spent on treating the late stages of illnesses which could be either cured early or better managed in the future by the use of cell therapies.⁴

Regenerative medicine has been a priority research area in the UK for a number of years. In 2005 the UK Government's Stem Cell Initiative (UKSCI) report set out its long-term vision and costed strategy for the therapeutic use of stem cells through to 2015.⁵ This was one of the first comprehensive strategies for developing regenerative medicine therapies and helped the UK become a world leader in the underpinning science and commercial development of cell therapy products. This strength is highlighted by the fact that of the 132 regenerative medicine companies registered within the EU in 2011, over 28% of them were located in the UK, compared to 25% in Germany, 13% in France and 6% in Spain.⁴ These companies create a growing economic benefit as they develop products to meet the needs of a global industry that is expected to be worth £4 billion by 2015, as well as promoting the growth of support companies developing related infrastructure for cell manufacture.

While the majority of regenerative medicine products have traditionally been developed by small companies (<250 employees with a turnover <£40 million), the field is now starting to attract the attention of large multinational pharmaceutical companies. In 2008 Pfizer opened its first dedicated regenerative medicine facility in Cambridge UK to investigate the use of stem cells to treat neurodegenerative disease. In 2010 Teva pharmaceutical completed a \$1.7 billion deal with therapy company Mesoblast for exclusive rights to their mesenchymal precursor stem cell platform for cardiovascular disease, stroke and various neurodegenerative indications. Then in 2012, the pharmaceutical company Shire purchased Advanced BioHealing for \$750m to give them access to their tissue-engineered skin substitute (Dermagraft) that is used to treat slow-healing foot ulcers.

This interest in regenerative medicine by the pharmaceutical industry is driven by:

1. The fact that regenerative medicine products can be targeted to a wide range of diseases and treatments (to date there are over 240 cell-based therapies in clinical development or on the market⁶).
2. The increasing evidence that regenerative medicine products can deliver safe and efficacious therapies that may be manufacturable at scale to allow them to compete with traditional drugs (over 500,000 people have so far been treated with regenerative medicine products).
3. The fact that regenerative medicine products can be used to create advanced cell models to test the efficacy and safety of small molecule drugs.

This third point is particularly important for the pharmaceutical industry where up to 80% of the cost of bringing a new drug to market (~\$1 billion) can be

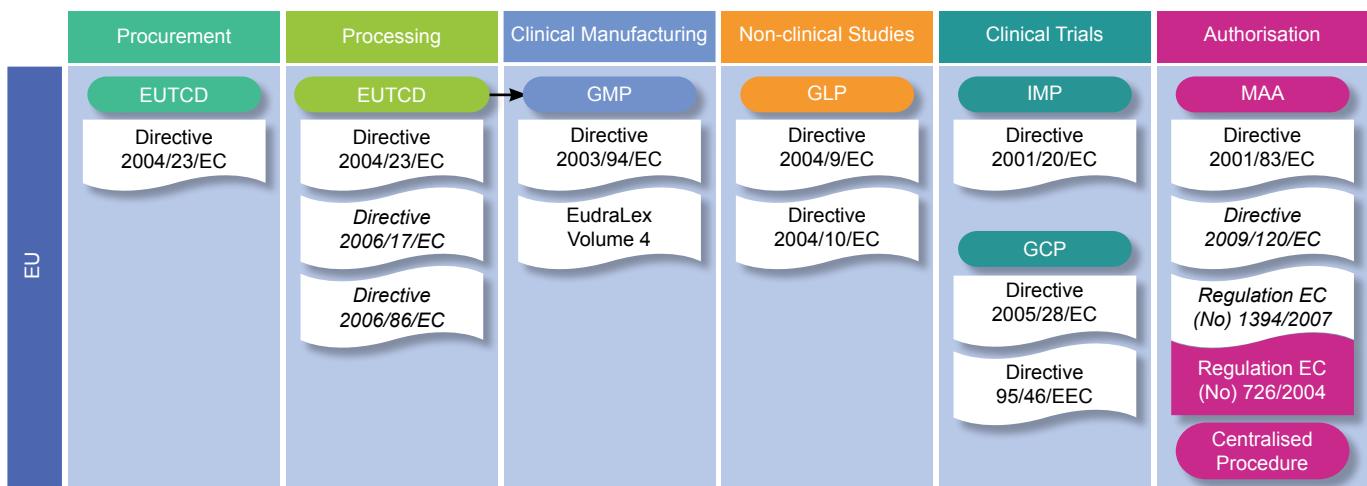


Figure 2. The range of EU directives and regulation which can apply to different phases of product development depending upon the cells used and their application (Figure taken from PAS 83:2012 (PAS 83 revision) “Developing human cells for clinical applications in the European Union and the United States of America”. Permission to reproduce extracts from PAS 83:2012 is granted by BSI. British Standards can be obtained in PDF or hard copy formats from the BSI online shop: www.bsigroup.com/shop or by contacting BSI Customer Services for hardcopies only: Tel: +44 (0)20 8996 9001, email: cservices@bsigroup.com).

associated with failed drugs that should have been deselected during cell based testing for safety and efficacy.

However, there are still major issues to be addressed to enable this nascent industry to truly flourish, especially with regard to supporting companies to allow them to comply with regulatory requirements for product development, manufacture and release. In the UK the regulatory pathway for regenerative medicines is generally considered to be well established. However, depending upon the source of the cellular material used and the extent to which it is manipulated during manufacture and/or before transplantation, a product could end up having to comply with several different directives and regulations (Figure 2). Furthermore, the unique properties of regenerative medicine products means there are no standard tests which can be used to support characterisation of the cells to comply with regulation and it is left to the companies developing the products to demonstrate their tests are sufficient. To address these challenges, standards development organisations such as the British Standards Institution (BSI) have been developing documentary guidelines to assist companies developing products to comply with regulations as they transit from the laboratory, through clinical trials, into manufacture and onto the market.

2. The role of Standards and Metrology

The importance of standardisation to support innovation driven markets was discussed in the paper “Standards can help bring cell therapy products to market”,⁷ which was co-authored by LGC and published by Bioprocess International in 2012. The paper highlights how the development of documentary standards and guidelines not only supports product developers but also provides confidence to

technology adopters and reduces barriers to trade. Indeed, evidence has shown that not considering standardisation for emerging technology leads to significant economic inefficiencies.⁸

As an industry changes and matures, the types of standards and guidelines it requires to gain a competitive advantage also change and the role of measurement science (metrology) to support product characterisation increases. For example, emergent industries gain most benefit from vocabulary standards which allow companies to speak a common language and communicate highly technical information to investors and future customers. Then as these emergent products begin to enter the marketplace there is an increased need for testing standards and a requirement for metrology to allow product testing and differentiation. This is where National Measurement Institutes (NMI) such as LGC can play a key role in developing the underpinning metrology to support testing strategies which act as enablers for UK companies to release their products onto the market. Once a range of products are established and a well-defined marketplace has developed, then the standardisation requirements shift to formal standards for product compatibility and product specifications. Again, metrology plays an import role here by developing traceable measurement techniques and reference materials to support product testing.

3. The role of LGC in regenerative medicine standardisation

As the UK’s designated NMI for chemical and bioanalytical measurement, LGC leads the development of the bio-measurement system, strengthening the traceability of measurement science that underpins legislation, regulation

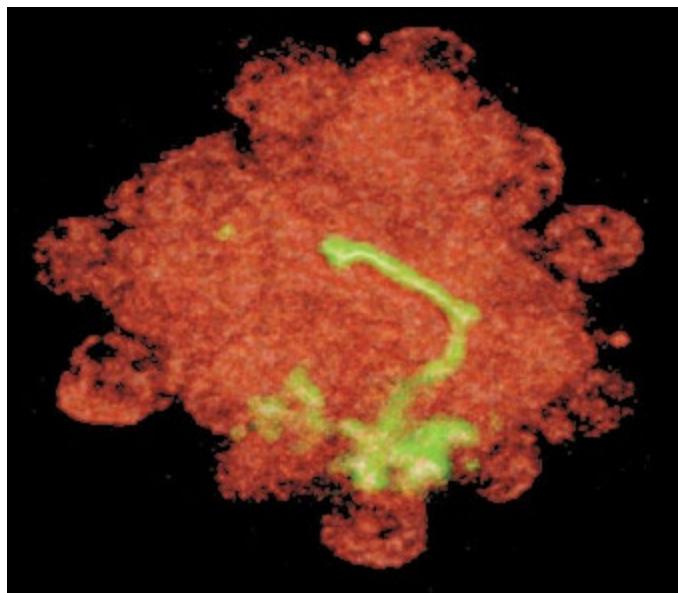


Figure 3. Human hepatocytes (liver cells) and bile canaliculi. This image is a 3D reconstruction of human hepatocytes (red) grown as a cluster in a culture vessel.

and standards, especially in the healthcare sector, including regenerative medicine.

LGC's capabilities in cell imaging have provided novel ways to measure cell activity in 3D structures that mimic *in vivo* conditions (Figure 3). LGC has successfully combined laser scanning confocal microscopy (LSCM) with fluorescent probes to enable the multiplexed analysis of cells within 3D tissue-engineered products. Different fluorescent probes can be combined to measure biological processes such as active metabolism, indicating viable cells, DNA intercalation indicating damaged or dead cells, and the production of reactive oxygen species, which is linked to cell stress. Using this approach, LGC scientists have demonstrated how cell viability and cell stress change during manufacturing, storage and transportation, providing valuable information to the tissue engineering industry to enable the optimisation of production and distribution processes.

To ensure that the measurement science expertise developed feeds through to the standardisation process, LGC experts work with BSI to develop written standards and guideline documentation for this sector at both the national and international level. These activities provide a valuable de-risking resource, particularly for emerging and early stage companies and researchers looking to define their product development pathway.

Within the UK, one mechanism to achieve rapid standardisation is to create a Publicly Available Specification (PAS). A PAS is similar to a formal standard, but its development uses a fast-track process enabling a rapidly developing market, such as regenerative medicine, to benefit from the standardisation process at a much earlier stage. The level of consensus required is not as stringent as that for a formal standard, with

the guidance being derived from the technical knowledge of a convened group of expert stakeholders.

Since 2006 there have been a total of 4 PAS documents (Figure 4) produced in the UK to support developers of regenerative medicine products and LGC has played a key role in each of these. The PAS documents can be freely obtained from the BSI website (www.bsigroup.com/shop).

PAS 83 “Guidance on codes of practice, standardised methods and regulations for cell-based therapeutics”

In 2006 LGC co-authored the first PAS document specifically designed to support developers of regenerative medicine products. The document defined, in the form of a process map, the key steps in a cell-based product lifecycle, from cell/tissue procurement through to commercialisation and post-launch activities. The main aims of the document were to:

- Provide clear guidance to industry on the extent of standardisation that should be used during the process of research, development, clinical trials and commercialisation of cell therapy products;
- Identify which regulations, codes of practice and standards are already available in this field and link them to the lifecycle of cell-based therapy product production.

PAS 83 provided regenerative medicine companies with a detailed process map which highlighted the critical stages involved in the product pathway, initiated by the procurement of cells or tissue. Each stage was accompanied by details of the legislative acts, the codes of practice and the guidance documents supporting the appropriate legislation. This allowed PAS 83 to act as a navigation tool to direct product developers to the relevant documents.

PAS 84 “Regenerative Medicine Glossary”

In 2008, a second PAS document was produced to support regenerative medicine companies. This document, again co-authored by LGC, took the form of a vocabulary standard designed to provide clear guidance on the meaning of terminology currently used within this field in the UK by industry, regulators, government and academia. PAS 84 was produced using the views and opinions of key UK stakeholders and was developed to act as an accompanying document to PAS 83.

In particular PAS 84 was intended to help UK stakeholders:

- Prepare for legal, commercial and societal issues;
- Facilitate a common understanding of the science of regenerative medicine;
- Improve communication and understanding of advances in the field;



Figure 4. The four regenerative medicine PAS documents to which LGC has contributed.

- Demonstrate best practice and product quality;
- Reduce research, development, production and transaction costs.

PAS 93 “Characterisation of human cells for clinical applications”

In 2011 LGC co-authored a third regenerative medicine PAS document in response to difficulties that were being encountered by companies obtaining market authorisation for cell-based products in Europe. In the EU, a medicinal product is one that is subject to the regulatory framework set out in European Directive 2001/83/EC for the authorisation, control and marketing of medicines. Medicinal products require prior approval from regulatory authorities before they can be used in clinical trials or sold in any country of the European Economic Area. For cell-based medicinal products it is more complex as they are classified as Advanced Therapy Medicinal Products (ATMP) and so are also subject to the specific provisions of the ATMP Regulation (EC) No 1394/2007. Such products therefore also require characterisation of their cellular component to facilitate consistent manufacture and ensure product quality. Due to the small number of cell-based ATMPs on the market,

routine measurement and characterisation techniques for these products have not yet been established. This means that it is difficult for companies to demonstrate that their products are of a consistent quality. Despite this, the regulatory agencies still require applicants to provide satisfactory answers to questions about cell identity, viability, number and the nature of any cellular impurities.

PAS 93 provides general guidance applicable to all cell therapy products and also guidance specific to licensed biologics and ATMPs. The document also contains a significant technical annex which used LGC's measurement expertise to provide guidance on the approaches which can be used by developers to characterise the cells in their regenerative medicine products.

PAS 83:2012 (PAS 83 revision) “Developing human cells for clinical applications in the European Union and the United States of America”

In 2012 a significant revision of PAS 83 was published. This revision was made to recognise changes that had occurred in the fast moving field of regenerative medicine since 2006, and to support companies in the development of products that

conform to regulations in the EU and in the main target market of the US. This revision identified the legal requirements and guidelines applicable to each stage of the product development process map and the regulations and guidelines already available in this field, and linked them to the lifecycle of the product. Each stage is accompanied by a set of bullet points informing users of important points of awareness and a list of the accompanying legislative acts and guidance documents supporting the legislation. In the case of the latter, it is intended that these be used as a navigation tool to direct the user to the relevant documents.

4. Conclusion

Standardisation is essential for ensuring the comparability and reliability of the measurements required to underpin all aspects of medical treatment. Rapidly developing areas based on new technologies, such as regenerative medicine, gain particular benefit from establishing sound reference and measurement frameworks at an early stage.

LGC, in its role as an NMI, plays a key role in the standardisation process, through the development of measurement procedures required to characterise products, and through the production of documentary standards, both of which support manufacturers. In the area of regenerative medicine, LGC has played an active role in establishing a standard vocabulary, and in agreeing the codes of measurement practice needed to bridge the gap between regulators and manufacturers of cell-based therapies. These will help developing and established companies alike to bring products to market more quickly, providing viable alternatives to conventional treatments. In turn, this will contribute to maintaining the UK's position as one of the technological leaders in this sector.

5. Acknowledgements

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