



A framework for standards to support innovation in cell therapy manufacturing

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Standards and Innovate UK

Innovate UK - the new name for the Technology Strategy Board - is the UK's innovation agency. Our aim is to accelerate economic growth by stimulating and supporting business-led innovation.

Timely, consensus-based use of standards plays a vital role in ensuring that the knowledge created in the UK's research base is commercialised and brought to market and plays an important part in driving innovation.

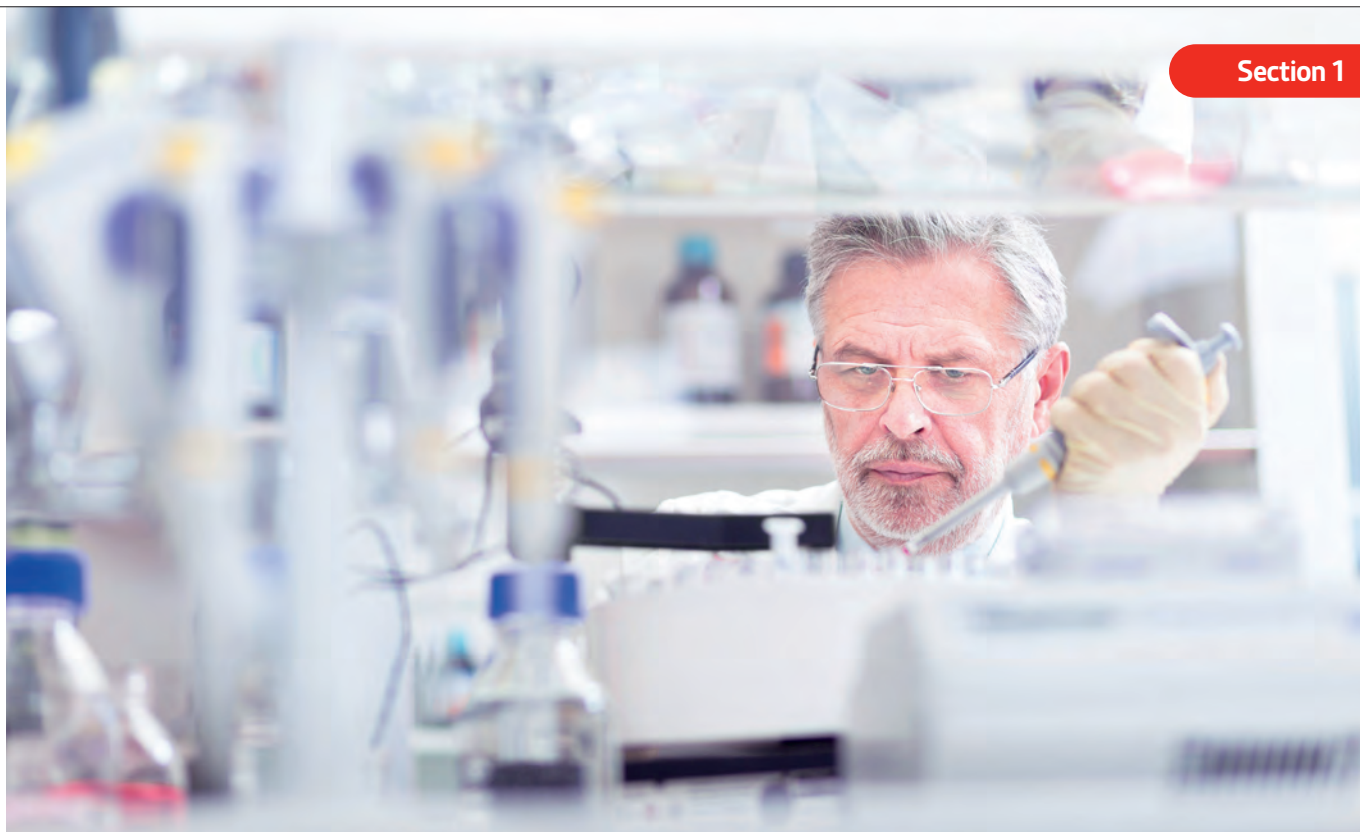
Innovate UK is working with BSI, Research Councils and Catapults to establish new standards earlier in the development of technologies, to provide UK businesses with a competitive "first mover advantage." We are focusing particularly on four emerging technology areas: offshore renewable energy, assisted living, cell therapy and the subject of this report, synthetic biology. Here the primary objective of the project is to enable computer aided design, manufacture, and verification using digital biological information.

We have also joined with the Engineering and Physical Sciences Research Council and Biotechnology and Biological Sciences Research Council to create SynbiCITE, a pioneering Innovation and Knowledge Centre dedicated to promoting the adoption and use of synthetic biology by industry. The centre is focused at Imperial College, London and will help turn academia and industry-based research into commercial success. For more information see <http://synbicite.com/>

More widely, health and care is a key priority area in our work - with major innovation programmes to stimulate the development of new technologies, products and services, building on the UK's world-class science and technology base and its global presence in the biopharmaceutical and health technology sectors. Read more here: <https://www.innovateuk.org/healthcare>.

For more general information about the Innovate UK please see: www.innovateuk.org or contact support@innovateuk.gov.uk.

Innovate UK
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The promise of cell therapies

Cell therapies and regenerative medicine offer great potential for significant wealth creation and enhanced quality of life by treating conditions and offering better outcomes than can be offered currently. The government and industry have made significant investments in this technology, and that has resulted in the UK being a potential world leader in its commercialisation and deployment. The Technology Strategy Board have set up the Cell Therapy Catapult, and its vision is:

“for the UK to be a global leader in the development, delivery and commercialisation of cell therapy, where businesses can start, grow and confidently develop cell therapies, delivering them to patients rapidly, efficiently and effectively.”

Many cell therapies are, or will be, classed as medicines, and so will need to comply with the relevant legislation. A major aspect of this is the adoption of the principles of Good Manufacturing Practice (GMP), as demonstrated in Europe through the EU GMP Guidelines¹. There has been, however, a shortage of new medicinal products reaching the marketplace due to problems relating to manufacturing and GMP compliance in Europe². It is essential that, if the industry is to avoid the situation where new cell therapies are not reaching the marketplace, and the enormous investments made by government and industry are not wasted, a better approach to consideration of manufacturing of cell therapies is developed.

Enhanced quality of life



Section 2



Medicines and Eroom's Law

The medicines industry has, over many years, experienced a decline in the output of new drugs emerging from its expensive R&D programmes³. The number of new drugs approved per billions US dollars spent on R&D has halved roughly every 9 years since 1950, an alarming example of increasing costs accompanying a fall in output. This fall in R&D productivity is, from some perspectives, quite puzzling, particularly when relevant technologies have evolved over that period and are vastly more efficient than they used to be.

For example, the following developments have occurred over this period:

DNA sequencing is now a billion times faster than in the 1970s

3D protein structure databases now have 300 times more entries than in the late 1980s

Using x-ray crystallography to determine a 3D protein structure now uses over 1,000 fewer man hours than it did in the 1960s

New fields have emerged, such as biotechnology, computational drug design, and transgenic mice

Despite all of these technical advances new drug output per billion US dollars spend on their development continues to fall. This decline is diametrically opposite to the rise in R&D productivity experienced by the semiconductor industry, through following Moore's Law. This has led to the situation in medicines developments as being subject to "Eroom's Law" (Eroom being 'Moore' spelt backwards).



Standardization and Moore's Law

The semiconductor industry is one whose rising productivity is enshrined in the concept known as "Moore's Law". This law arises from the prediction by Gordon Moore⁴, of Intel, that the number of transistors per unit area of silicon will double every 2 years. This prediction has proven to be resilient, and the R&D productivity of the silicon industry continues to grow in line with this forecast.

This rise in productivity has been critically dependent upon the development of standards, particularly those under the auspices of SEMI, the industry trade association. SEMI developed a large range of standards, particularly with regards to silicon wafers, automation, and computing⁵.

The business models of the semiconductor industry have changed dramatically since the mid-1960s⁶. In the early stages, companies such as Texas Instruments and Intel would manufacture their own silicon, leading to widespread variability in the condition, crystal orientation, and composition of wafers. In the 1970s, standardization led to the development of specialist silicon suppliers, thus increasing

the length of the supply chain, leading to increased specialisation, which in turn led to high productivity. This specialisation increased in the 1980s with the emergence of 'fabless' design houses, and specialist contract foundries. The SEMI standards developed for the industry were critical in allowing these companies to diversify and specialise in this way.

Thus, the semiconductor industry is an exemplar for how active standardization has enabled significant R&D productivity growth to occur, and one other industries can learn from.

The challenge for the medicines industry is to reverse the prevailing trend in that sector, and to start developing new drugs at a rate that exhibits similar characteristics to the semiconductor industry.

Active standardization enables
significant productivity growth

Section 4



Innovation in manufacturing

Innovation in manufacturing systems has been a major contributor to wealth creation since the industrial revolution, and such innovations have been contributing to improving productivity ever since⁷.

Innovations in manufacturing systems include the development of new paradigms building on mass manufacturing, including the following:

Lean production

Mass customisation

Time-based manufacturing

Agile manufacturing

Each of these contribute to rises in productivity, either through increased efficiencies in the use of material or time, or responding quickly to changing customer needs. An paper by Griffiths⁸ demonstrates how each of these developments critically depended on the emergence of the right standards. For example, the shift from a craft-based system to mass manufacture required interchangeable parts, which requires a significant degree of standardization. Henry Ford was a major innovator in this regard, and his pioneering of interchangeable parts at the manufacturing stage led to his company revolutionising personal transport, and creating large amounts of wealth at the same time.

At the very heart of all these systems is the concept of Design for Manufacture (DFM). DFM is the discipline of design of the manufacture of a product to reduce costs and improve productivity. The principle has been used in a number of different manufacturing disciplines, including printed circuit boards, automotive manufacture, and integrated circuits. A good example of best practice in this area is PD 6470:1981⁹, a document published in 1981 by BSI. This details in a non-prescriptive way, how best to organise the processes involved in mechanical and electrical manufacturing to boost productivity and efficiency.





Section 5



Manufacturing design for biopharmaceuticals

Lonza Biologics, a major global contract manufacturer in the biopharma industry, have recognised that a lack of good practice in manufacturing design is a major issue, and have published papers¹⁰ describing this, and their vision of how this could be improved. A major contribution of theirs so far has been the introduction of the concept of 'developability'. Developability is a risk assessment at the early stages of development that has the intention of improving the probability of eventual success by designing products and processes with the right quality characteristics. The assessment focusses on analysis of the likely safety of the product and the ability to scale up manufacturing successfully.

One focus of attention more broadly applied to medicines is the gradual introduction of a concept known as "Quality by Design", or QbD. The intention with such an approach is that good quality processes are design and planned for, but the concept so far has been applied post-hoc and used more to validate processes rather than design them. The principles behind QbD, however, are fully compatible with the principles of DFM.

A criticism of existing process design is that successful ones occur randomly, through the application of sufficient spending arriving at a high quality, repeatable process. This satisfies regulatory requirements through trial and error, rather than through good design. This results in a situation where Eroom's Law dominates, and productivity falls over time, rather than rises. The challenge is to improve the output of new cell therapy products through increasing R&D productivity, thus increasing the probability of regulatory success by introducing principles of good manufacturing design into the cell therapy industry.

Quality by design



Design for manufacture – the role of standards

As shown previously, the output of new products of the cell therapy and biopharmaceutical industry could well be improved by wider adoption of design for manufacture principles. The challenge now is to establish how a standards development organisation, such as BSI, can be instrumental in enabling the industry to improve its design for manufacture practices.

BSI has already published a number of standards to enable DFM in the mechanical and electrical sectors, under the auspices of its technical committee TDW/4/7 Technical Product Realization - BS 8887 Design for MADE. The published standards currently available in this area include:

- **BS 8887-1:2006** Design for manufacture, assembly, disassembly and end-of-life processing (MADE). General concepts, process and requirements
- **BS 8887-2:2009** Design for manufacture, assembly, disassembly and end-of-life processing (MADE). Terms and definitions
- **BS 8887-240:2011** Design for manufacture, assembly, disassembly and end-of-life processing (MADE) – Reconditioning
- **BS 8887-220: 2010** Design for manufacture, assembly, disassembly and end-of-life processing (MADE). The process of remanufacture. Specification
- **BS 8887-211:2012** Design for manufacture, assembly, disassembly and end-of-life processing (MADE) - Specification for reworking and remarketing of computing hardware
- **BS 7000-2:2008** Design management systems - Guide to managing the design of manufactured products
- **BS 7373-1:2001** Guide to the preparation of specifications
- **BS 7373-2:2001** Product specifications - Guide to identifying criteria for a product specification and to declaring product conformity
- **BS 7373-3:2005** Product specifications - Guide to identifying criteria for specifying a service offering
- **PD CEN/TS 16524:2013** Mechanical products. Methodology for reduction of environmental impacts in product design and development
- **PD 6470:1981** The management of design for economic production. Standardization philosophy aimed at improving the performance of the electrical and mechanical manufacturing sectors.

Section 6



Improve design for manufacture practices

The philosophy, first pioneered by PD 6470:1981 to reduce manufacturing costs in the mechanical and electrical sectors, has been extended to add value in a number of different ways. It has evolved and BSI has now published best practice in Design for Manufacturing, Assembly, Disassembly, and End-of-Life Processing (MADE). This is appropriate to all manufacturing sectors and enables the identification of ISO Standards relevant to the design for manufacture. It provides the designer with a framework for the selection, preparation and presentation of appropriate documentation, so that the design concept can be transferred into and beyond the manufacturing environment. This is enabling major leaps forward to be made, including more efficient processes, reduced waste at end of life, and less costly reuse of parts.

Additionally the DFM approach means manufacturers can design processes that reduce their environmental impact, and extend their offering through service innovation. A natural step is to apply this philosophy to the design of high quality, repeatable cell therapy manufacturing processes.

BSI has already published 3 current documents that can directly be applied to this problem:

- **PAS 83:2012** Developing human cells for clinical applications in the European Union and the United States of America. Guide
- **PAS 84:2012** Cell therapy and regenerative medicine. Glossary
- **PAS 93:2011** Characterization of human cells for clinical applications. Guide.

In addition, BSI has won approval to work with cell therapy stakeholders to develop best practice in the selection of raw materials to improve the quality of manufacturing processes. What is lacking is an overall approach to the development of the appropriate guidance in solving this problem, and a programme of work to put the appropriate knowledge into place.



A standards framework for cell therapy manufacturing

The required framework for standards for cell therapy manufacturing would have the following intentions:

- To improve the probability of regulatory success by enabling product developers to design higher quality and more repeatable manufacturing processes;
- To increase the number of cell therapy products available on the market;
- To reduce the investment costs required to successfully put a product onto the market.

The framework would work by applying the philosophy of design for manufacture into the cell therapy industry, and develop the appropriate best practice to enable this. To achieve this vision requires the co-operation and participation of all major stakeholders in the cell therapy industry, and their commitment to the development and distribution of best practice in cell therapy manufacturing process design.



Contact us to find out how BSI helps to make excellence a habit.

Footnotes

1. These guidelines contain information relating to the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively.
2. Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems – European Medicines Agency, November 22nd 2012.
3. Diagnosing the decline in pharmaceutical R&D efficiency, Jack W. Scannell, Alex Blanckley, Helen Boldon & Brian Warrington, Nature Reviews Drug Discovery 11, 191-200 (March 2012).
4. Cramming More Components onto Integrated Circuits, Gordon Moore, Electronics, pp. 114–117, April 19, 1965.
5. "About SEMI" - <http://www.semi.org/en/About/P001455>
6. E-Business and the Semiconductor Industry Value Chain: Implications for Vertical Specialization and Integrated Semiconductor Manufacturers, Jeffrey T. Macher, David C. Mowery, Timothy S. Simcoe, East-West Center Working Papers.
7. Towards a conceptual framework of manufacturing paradigms, W. G. K. Lee, T. Baines, B. Tjahjono, and R. Greenough, SIMTech technical reports, Volume 7 Number 3 Jul-Sep 2006.
8. Manufacturing paradigms: the role of standards in the past, the present and the future paradigm of sustainable manufacturing, Brian Griffiths, Proc IMechE – Proceedings of the Institution of Mechanical Engineers, Part B: Journal of Engineering Manufacture October 2012 226: 1628-1634, first published on May 30, 2012.
9. PD 6470 - The management of design for economic production. Standardization philosophy, aimed at improving the performance of the electrical and mechanical manufacturing sectors.
10. Developability assessment as an early de-risking tool for biopharmaceutical development, Jesús Zurdo, Pharmaceutical Bioprocessing April 2013, Vol. 1, No. 1, Pages 29-50.



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