BIA Manufacturing Advisory Committee (MAC) workshop report - "Next Generation Analytics"

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Introduction

Biopharmaceuticals including monoclonal antibodies, therapeutic proteins, vaccines, viral based gene therapies and cell therapies are the most sophisticated and complex drugs ever developed. In many cases these therapeutic modalities have high efficacy and specificity allowing them to target disease that have traditionally been untreatable. The UK is a leading player in the development of biopharmaceutical drugs with annual government spending on health research and development of £3 billion, which comes on top of an industry spend of £4.3 billion [1]. This has created a thriving ecosystem in the UK which is contributing to over 1000 current clinical trials and the highest number of academic citations of any European nation[2].

Despite strong growth in the biopharmaceutical sector over the last decade there are a number of manufacturing challenges that need to be addressed to ensure the UK maintains its leading position. The first challenge is adapting to a continually evolving landscape where new and more sophisticated treatment architypes are being developed. These include, bi-specific drugs, antibody-drug conjugates, genetically edited therapies and highly personalised cell therapies uniquely tailored to an individual patient. These new therapies can give rise to biopharmaceutical products with N-of-1 production runs, highly specific manufacturing requirements and genotype-specific processes. Unsurprisingly, this fundamental shift in the overall product mix alongside increasing market competition is driving a need for new and innovative approaches to the way these products are made.

Price is also a challenge. The innovative and complex manufacturing processes required to produce biopharmaceutical drugs often means they are charged at a premium. Drug prices can range from tens of thousands of pounds for monoclonal antibodies, through to hundreds of thousands for CAR-T immunotherapies and even millions of pounds for some *in-vivo* gene therapies. While these prices represent the value that the therapies bring to patients, the manufacturing processes are often a significant component of the overall cost-of-goods. Consequently, there is a drive for more efficient, controllable and scalable processes to ensure these treatments remain competitive. This is particularly pertinent as downward cost pressure continues to intensify as healthcare systems struggle to balance rising demand with flat or declining budgets. For cell and gene therapies these pressures have already led to the implementation of new drug reimbursement models. These include "payment-over-time" which allow insurers to amortise the cost of therapies over several years and "Pay-for-performance"

[1] Office for Life Sciences – Life science competitive indicators 2019.
[2] Dept for Business, Innovation and Skills - Performance of the UK research base: international comparison.

which benchmarks payments based on positive health outcomes, with rebates if therapies are not as efficacious as expected.

Manufacture of large biological drugs and viruses at industrial scale is not only costly, it is also complex with production runs for a single batch often taking several weeks. The robustness of the manufacturing process is also intrinsically linked to the quality of the drug product and can lead to post-translational modifications and degradation products which affect the efficacy and safety of the drug. The complexity of manufacturing and its impact on product quality is perhaps even greater for cell-based therapies where the trajectory of cell phenotypic fate is often directly influenced at the genomic, epigenomic and proteomic level by the bioprocessing environment. Consequently, it is becoming increasingly important to try and attain a high level of process control to minimise any negative impact from the culture environment on the final quality of the drug product.

The integration of technologies to measure cell behaviour during bioprocessing is fundamental to ensuring the high levels of control required to maintain drug quality at industrial scale. However, determining critical quality attributes and reliably monitoring them is often difficult as they are rarely univariate and often subtle. This makes the accuracy and sensitivity of analytical measurement crucial. Challenge also comes from the fact that many of the analytical technologies that are used to measure quality attributes are not 'process-ready' which can limit their application for data-driven decision-making.

A further challenge on the horizon for biopharmaceutical manufacturing is the "fourth industrial revolution" or "Industry 4.0.". The first industrial revolution introduced mechanical production; the second, mass production; and the third, automation of production. Industry 4.0 is characterised by cyber-physical systems and machine-to-machine communication via the Internet of things (IoT). At the heart of industry 4.0 is the intelligent, smart factory which uses advanced sensors and information technologies to generate, collect and interpret large amount of production related data. This requires "big data" processing technology to build an integrated environment in which the entire production process can be represented, controlled and managed in a highly efficient way. The UK is in a strong position to gain competitive advantage through the implantation of an industry 4.0 paradigm. This is due to its world class network of innovation centres, measurement system (metrology) laboratories, academic hubs and industry focused organisation which could coordinate activities at a national level. These include the Medicines Manufacturing Industry Partnership (MMIP), which has workstreams focused on key enablers of advanced manufacturing such as:

Technology and innovation – which provides strategic investment to support the exponential growth in new technologies and equipment connectivity to ensure they meet the future needs of the medicines industry.

Advanced therapies manufacturing – which is ensuring the UK maintains a leading position in the global advanced therapies sector and is providing a platform for the development of relevant skills to exploit emerging manufacturing technologies.

Regulatory environment – which is maximising the potential of a standards, measurement (metrology) and accreditation infrastructure and innovation ecosystem which ensures there is a flexible regulatory landscape which can support accelerated growth within the biopharmaceutical industry.

This network can underpin the development of the technologies, skills, data and a supportive regulatory environment that will be required to achieve true disruption to traditional ways of manufacturing products while ensuring rigorous tolerances for product quality are maintained.

The challenge:

The emerging technologies that characterise Industry 4.0— data connectivity, advanced analytics, robotics and automation—have the potential to revolutionise every element of biopharmaceutical manufacturing within the next five to ten years.

The UK must provide an environment which supports the fast-evolving biopharmaceutical sector while allowing analytical and digital technology developers to innovate, implement and adapt systems to support future growth of the industry.

Addressing the challenge:

To address the challenge the BIA Manufacturing Advisory Committee (BIA MAC), supported by Cell and Gene Therapy Catapult and the Knowledge Transfer Network, held a workshop in June 2019 to discuss key challenges, barriers and opportunities for the development and integration of analytical technologies to support advanced manufacturing. The workshop which was attended by representatives from large pharma, biopharmaceutical SME's, technology developers, national measurement laboratories, RTO's and CDMO/CRO's (see appendix 1) discussed what analytical innovation is needed to accelerate growth within the industry.

The workshop produced a 10-year roadmap for the development and integration of analytical technologies to support the biopharmaceutical industry in a transition towards autonomous manufacturing using industry 4.0 principles (Figure 1). The roadmap shows how data-driven bio-manufacturing could be used to increase product knowledge, increase process automation, improve competitiveness and reduce overall costs of production. This is achieved through three steps:

1. Technology integration and the development of new bio-sensors with associated data analytics to allow a mechanistic understanding of process performance.
2. The development of adaptive manufacturing processes which can adjust to process variables to maintain tight control of product quality. This will be supported by advancement in the use of Internet-of-Things (IoT) technologies and increases in data-driven bioprocessing.
3. The use of analytics for fully connected real time data sharing and autonomous manufacture with minimal human intervention. This final stage could also facilitate disruptive approaches for product quality control testing through the implementation of real-time release testing strategies.

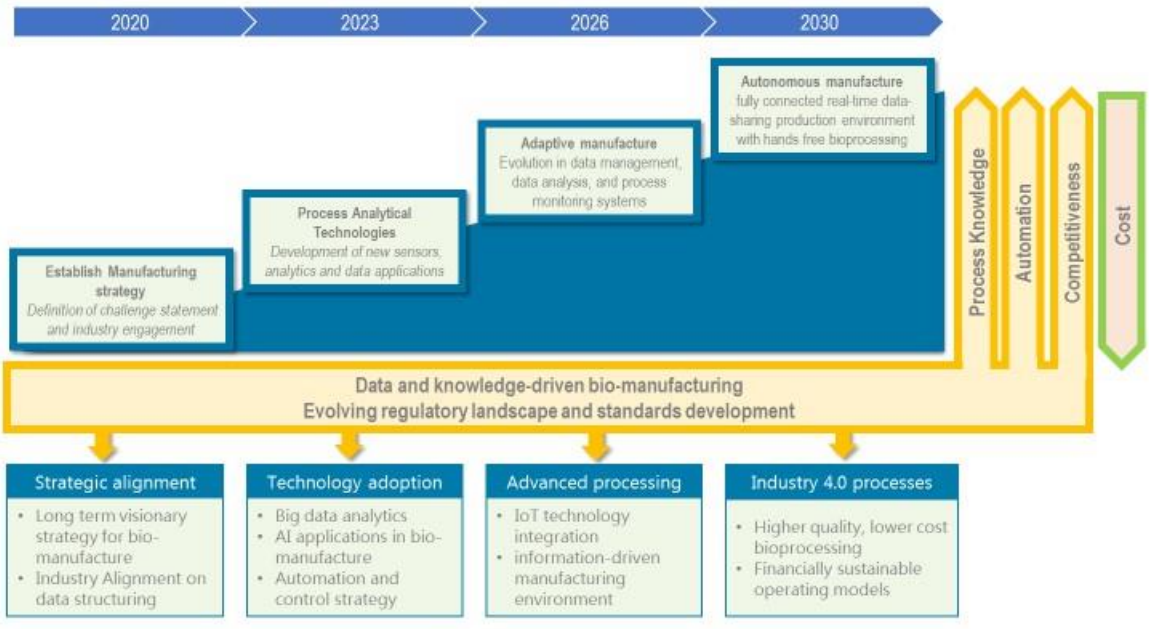

Figure 1 – 10-year roadmap for the integration of analytical technologies to facilitate advanced control during biopharmaceutical manufacture.

Based on this roadmap the consortium recommended that analytical integration for advanced manufacturing should focus on 4 key areas:

- *Supporting the development of Process Analytical Technologies (PAT)*

  PAT is a framework launched by the FDA in 2004 for "*designing, analysing and controlling the manufacturing process through the measurement of critical quality and performance attributes with the goal of ensuring final product quality*".[3] The aim of PAT is to encourage the adoption of more advanced in-process monitoring, particularly using measurement technologies that permit in-line or at-line analysis of key variables throughout the manufacturing process. Of particular importance are PAT technologies that allow real-time monitoring of a manufacturing platform using in-line sensors, as these can provide quality assurance during final manufacture while also allowing systems to remain closed, thereby minimising the risk of contamination. An important potential advantage of PAT for biopharmaceutical manufacture is the provision of process information in a time frame sufficient to allow proactive decision making. This has the potential to allow a tighter level of control over complex manufacturing processes and allow the early detection of poor process performance.

  Increasing adoption of the principles of PAT within the biopharmaceutical sector has fuelled a significant increase in the development of innovative new technologies for measuring process parameters in real time. However, many of the current PAT technologies are focussed on relatively simple parameters such as pH, DO, glucose and biomass. To build on the current foundations of PAT, innovation in sensor technologies needs to focus on measuring a wider range of critical quality attributes. This will be a significant challenge as all bioprocesses exhibit

[3] www.fda.gov/downloads/drugs/guidances/ucm070305.pdf, 2004

nonlinear dynamic behaviours which are dependent on unknown reaction kinetics. Therefore, a closer collaboration between drug developers and technology innovators is needed to drive continued improvements in sensor technologies and help bioprocess engineers achieve a holistic understanding of their processes and their correlations to product quality.

- *Supporting the digitally enabled horizon*

  Advancements in bio-manufacturing are increasingly data driven, using information derived from a wide range of sources to model and predict process performance. Some large pharmaceutical companies are now using advanced real-time data analytics and ongoing process verification to monitor processes, track trends, prevent deviations and optimise scheduling. All data processing can be done in near real time with data access made available to process teams anywhere around the world.

  Laboratories that transition to being digitally enabled have been shown to be more productive with the ability to implement operations that are more agile and responsive. This can include significant reductions in manual documentation, improved compliance from reduced errors and variability, as well as seamless data retrieval and analysis. For example, Merck recently developed a data system called MANTIS (Manufacturing and Analytics Intelligence System) that allowed them to reduce the cost of analytics projects by 45% and increase productivity by 30% using an advanced modular and scalable digital-twin platform to predict impacts before making physical changes. They also used advanced analytics to reduce deviations by 80 percent, eliminating reoccurring deviations altogether and accelerating deviation closure by 90 percent.[4]

  Digital enabling the manufacturing environment can be achieved using off-the-shelf technologies. However, there isn't a one-size fits all approach for integrating real time data analytics which makes the return on investment hard to justify for all but a few larger organisations. As a result, most companies are capturing only a fraction of the potential value of the data and analytics associated with their manufacturing process. The challenge is how to unlock data-driven opportunities for companies at all stages of drug development to act as a catalyst for future innovation.

- *Real time release testing*

  Real time release testing (RTRT) is a framework to ensure the quality, safety and efficacy of the final drug product based on data generated during the process. This typically includes the measurement of CQA's during the process in combination with real-time monitoring of process parameters to generate data which can be reliably used for mechanistic, empirical, or semi-empirical modelling to demonstrate product quality. RTRT approaches have been applied for biopharmaceutical manufacture to measure CQA's relating to the physical and chemical properties of the therapeutic protein (charge, aggregation, glycosylation etc.). However, for cell therapies CQA's are likely to be more complex, involving cell phenotyping, biomarker quantification and functional cell testing. These can involve challenging and time-consuming assays performed on small sample volumes which require specialist data interpretation. Therefore, to enable RTRT implementation across the biopharmaceutical field, new analytical platforms are required that allow limited sample handling, are fully automatable, are fast relative to the process dynamics, and can be qualified and validated for use in a GMP facility.

[4] CIO report - Merck manufacturing and IT (https://www.cio.com/cio100/detail/2758)

- *Standardisation*

  Standardisation is essential in supporting the future development of intelligent industrial manufacturing systems which can be adopted at a global scale. Standardisation comes in various forms:

  - Non-governmental standards setting bodies such as the British Standards Institute (BSI) and International Organisation for Standardisation (ISO) play a key role in ensuring commonality in specification for products and services, thereby facilitating market simplification and international trade. For biotechnology processing applications, analytical method characterisation and data processing, ISO have a technical committee (ISO/TC 276) that is focussed on producing guides and documentary standards to help drive product development. This committee has so far produced 7 standards relating to ancillary material testing (3 standards), cell counting (2 standards), nucleic acid quantification (1 standard) and biobanking (1 standard) and has a further 21 standards at various stages of development.
  - Communication standards organisations will also play a role in ensuring that systems and technologies can talk to each other in a plug-and-play manner. This may involve adopting interpretability standards from organisations such as the OPC Foundation and data exchange standards from the International Electrotechnical Commission. These standards will be increasingly important as machines communicate directly with each other, with less human involvement.
  - National measurement laboratories can support industry through the provision of reference methods and physical reference materials to ensure traceability and measurement competency. Where required these reference standards can be distributed through certified producers to facilities around the world.

Together these different forms of standards help ensure quality is maintained by demonstrating comparability across international borders. The UK can, and does, play a leading role in supporting standardisation and accreditation which, over the coming years, can be leveraged to support advanced manufacturing and provide competitive advantage for UK companies and innovators.

Across the board, transformational innovation is needed. Developments in new instrumentation, techniques and processes are key areas that companies need to focus on to ensure future growth. Analytical and digital innovation is needed that delivers excellence across the biopharmaceutical workflow, from drug development and process optimisation through to manufacturing, formulation and QC. As competition increases and the need for cost reductions become more apparent there will be an increasing drive for technology integration that can start adding value the from the moment it is installed.

A national approach to analytical innovation

Investment into advanced data analytics and digitisation is a central theme in the UK government Industrial strategy[5] with a commitment to support sectors to boost their productivity through the Industrial Strategy Challenge Fund (ISCF). Creating networks to harmonise national expertise and make the UK a global leader in industrial digital technologies is also a specific recommendation in the 2017 "Made Smarter" review.[6]

Enabling analytical innovation to support the development of an industry 4.0 architecture for advance biopharmaceutical manufacturing will require unprecedented levels of pan-industry collaboration. However, the UK is ideally positioned to address this challenge through its established infrastructure of world class facilities providing access to unique knowledge, skills and expertise (Figure 2). These include:

Innovation Centres: Providing access to complementary capabilities for commercial scale bioprocess development (CGT Catapult and NBMC), vaccine manufacture (VMIC), drug characterisation (MD Catapult and MMIC), data exploitation (Digital Catapult) and national measurement infrastructure support (LGC and NPL)

Standardisation: National certified reference material producers (including NIBSC), analytical monographs (British Pharmacopoeia), documentary standards and guidance (BSI and ISO)

Drug developers: The UK network of >2,000 biopharmaceutical companies comprising large pharmaceutical organisations and SME's, all underpinned by >1,400 support companies[7]

Digital innovations: UK companies specialising in digital platforms for manufacturing data management, physical digital integration, IoT and AI applications.

Universities: UKRI funded doctoral training centres specialising in bioprocessing, digital technologies and AI applications, EPSRC funded research "Hubs" and academic key opinion leaders.

Regulatory agencies: The UK Medicines and Healthcare products Regulatory Authority (MHRA) in collaboration with key international partners in Europe (EMA), the USA (FDA) and Japan (PDMA)

[5] HM Government Industrial strategy – Building a Britain fit for the future
[6] Made Smarter Review – Dept for Business, Energy and Industrial Strategy 2017
[7] UK Biopharmaceutical sector – opportunities and strengths. Office for Life Sciences report 2018

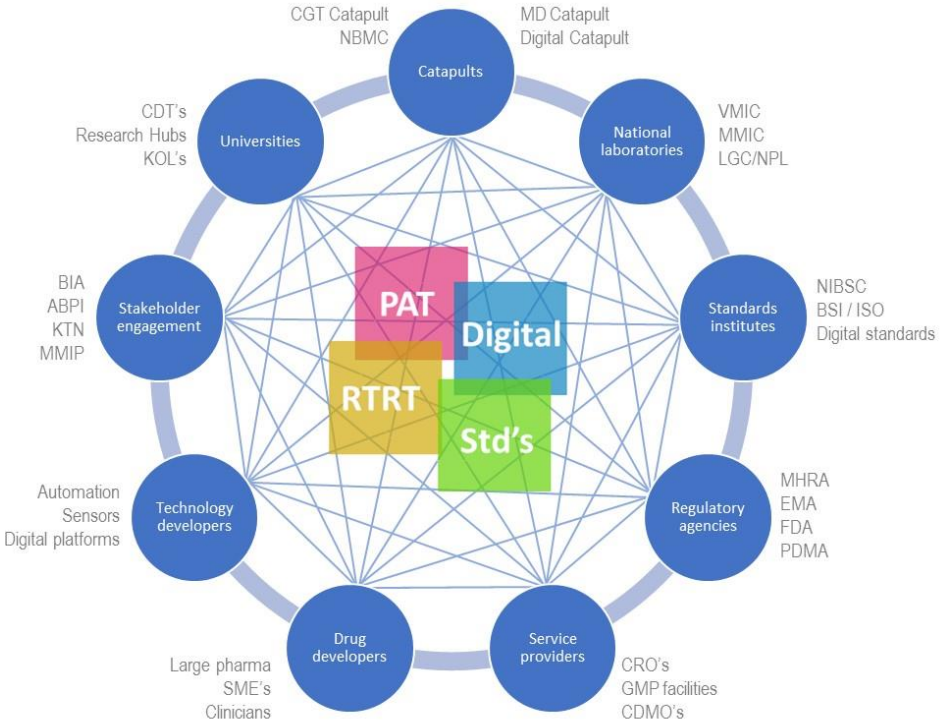

Figure 2 – The UK network of drug developers, national laboratories, standards organisations, regulatory authorities, universities and technology developers that can be used to deliver the 4 key themes which will underpin industry 4.0 for biopharmaceutical manufacture.

This network of UK national assets can act as the foundation for innovation "sandpits" which will drive the development of new technologies and new manufacturing practices to support the transition towards advanced manufacturing, increased process control and disruptive methods for product release.

Enabling the analytical innovation network

Enabling the UK to be leader in the advanced manufacturing of high value biopharmaceutical drugs requires an environment that promotes collaboration and risk taking to allow the development of transformative approaches. This must go beyond the scope of previous initiatives to ensure that advanced analytics can impact across the whole biopharmaceutical sector. To achieve this the workshop delegates made 4 key recommendations:

1. Create a 5-year programme to enable the biopharmaceutical industry to integrate Analytics for Advanced Bioprocess Control (Analytics ABC network). The network should be jointly funded by UKRI and industry to promote innovation and allow disruptive technologies to be developed which can give UK industry a competitive advantage. The proposed model is for open innovation calls under the four core themes identified in the workshop (PAT, digitisation, RTRT and standards) with collaborative projects running for 1-3 years. The aim of the programme over the initial 5-year period will be to develop the enabling technologies and digital infrastructure to support adaptive manufacture (as per Figure 1) which can be made available to wider industry through innovation "sandpits". It is anticipated that this

programme of work will require an investment of £30 million (£15M from UKRI and £15M from industry)

2. Establish an advanced analytics committee through the Bioindustry Association (BIA) with representation from all relevant stakeholders. The committee will also ensure the output from the collaborative projects are shared throughout the UK network.
3. Ensure there is comprehensive buy-in for the advanced analytics programme within the biopharmaceutical, digital and academic sectors through engagement with stakeholder organisations such as BIA, ABPI, KTN and MMIP.
4. Maintain close links with standardisation organisations such as BSI/ISO, NIBSC and BP, as well as national measurement (metrology) laboratories such as LGC and NPL, and the regulatory authorities to ensure documentary standards, reference methods and physical standards can be used to accelerate innovation.

The structure of the proposed programme is shown in Figure 3.

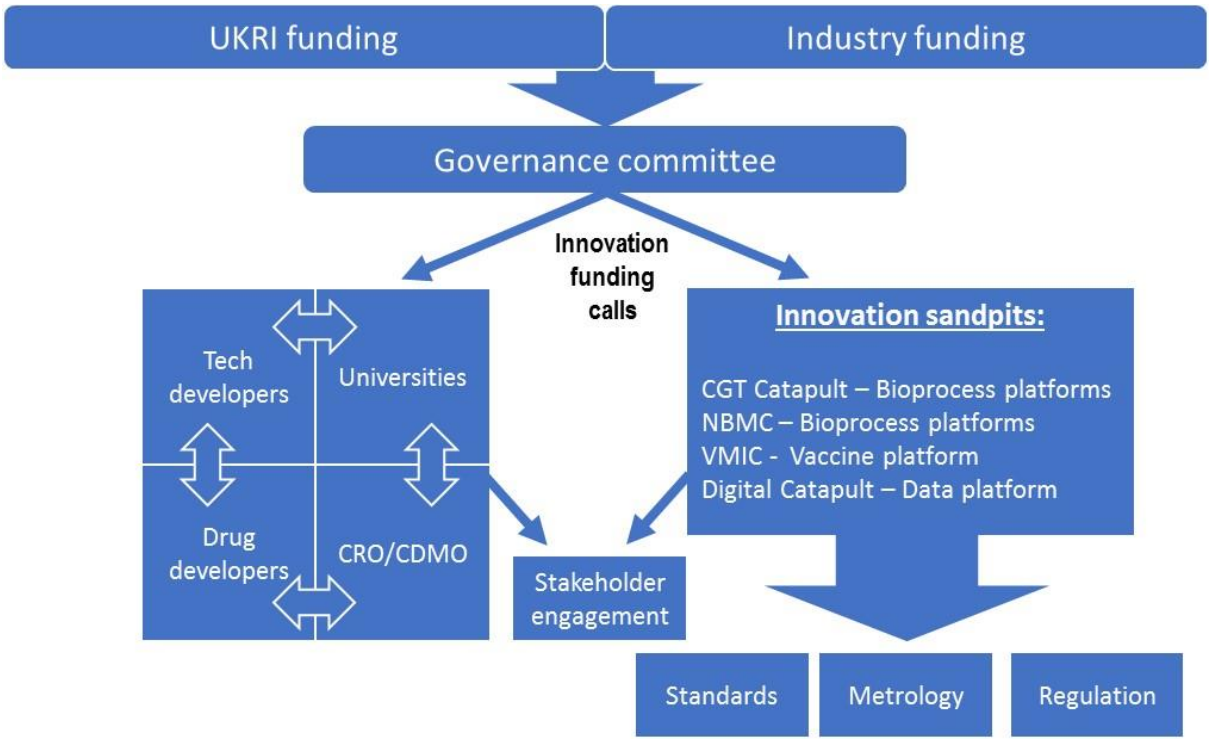

Figure 3 – Proposed structure of the advanced analytics network which will run as 5-year programme to deliver adaptive manufacturing platforms.

As highlighted in the industrial strategy the UK is "*extraordinarily well-placed to benefit from the new industrial revolution, with an enterprising economy built on invention, innovation and competition*". However, ensuring this potential is fully realised within the biopharmaceuticals sector requires rapid actions to allow UK companies to develop the next-generation of manufacturing platforms. Programmes such as the one proposed here can facilitate this move towards Industry 4.0 and act as a catalyst for inward investment into UK drug manufacture. This will open-up new opportunities for digital integration, enhancing a sector that already employs >150,000 people as well as increasing patient access to these new and highly efficacious therapies and treatments.

Report end.