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Department of Health
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25/04/2016

Dear Minister,

The UK landscape for regenerative medicine

Following publication of the Regenerative Medicine Expert Group (RMEG) report *Building on our own potential: a UK pathway for regenerative medicine* in March 2015, Ministers asked that the Chief Executives from the key delivery organisations should monitor implementation of the report's 20 recommendations (Annex A) to enable the routine use of regenerative medicine and other Advanced Therapies in the NHS and provide an annual report on progress. We are pleased to be able to provide you with an update on the progress over the past 12 months. We have also taken the opportunity to provide an insight into wider activity in the sector and how regenerative medicine is developing in the UK.

Overall, we feel that there has been considerable progress since the publication of the RMEG report. Regenerative therapies are now beginning to show significant clinical potential and there has been a rapid expansion in this sector in the UK. Many of the potential barriers to developing a commercial Advanced Therapy sector identified in the RMEG report have been resolved or are being actively addressed. This is due in no small way to the significant level of coordination, from research through to clinical use, which has meant that the UK is developing a world-wide reputation in the sector. There is also evidence of an active and developing community in regenerative medicines in the UK through organisations such as the ATMP Manufacturing Community and the London Regenerative Medicines Network.

The opening of the Cell and Gene Therapy Catapult Manufacturing Centre in 2017 will reinforce the UK as a global leader in the manufacture of Advanced Therapies. The Centre is a further element of the ambition stated by the Government in 2012 to develop the UK as a global leader in the development, delivery and commercialisation of Advanced Therapies. The Manufacturing Centre is part of an overall strategy to

create an environment where businesses can start, grow and confidently develop Advanced Therapies, supporting rapid, efficient and effective delivery to patients. Already some companies have expressed an interest to co-locate on the site with the Manufacturing Centre. The potential for regenerative medicine appears close to being realised, with the first of the next generation of curative therapies just entering the clinic.

One important issue that the RMEG report raised was the level of uncertainty regarding the regulation and approval process for these advanced therapies. The Medicines and Healthcare Products Regulatory Agency (MHRA) has taken a lead role in developing improved regulatory support. This includes developing a system that recognises individual products often require approval from a number of regulators (for example as they are derived from human tissues or are genetically modified) through the creation of a specific unified point of access for regulatory advice. After one year of operation, the Regulatory Advice Service for Regenerative Medicine (one-stop-shop) is handling increasing numbers of enquiries. In addition, the Medical Research Council has continued to develop and refine the UK Stem Cell Tool Kit that provides a reference tool for those who wish to develop a programme of human stem cell research and manufacture, ultimately leading to clinical application.

The MHRA continues to help shape the regulatory landscape and supports the work of the European Medicines Agency (EMA) as it further develops the regulatory framework for advanced-therapy medicinal products (ATMPs) that covers most regenerative medicine therapies. The ability of the MHRA to provide high quality scientific advice consistent with the EMA means that the UK is well-placed relative to other European countries. This has helped confirm the MHRA's global reputation for being willing to work with scientists and industry to support the introduction of innovative medicines.

The Cell and Gene Therapy (CGT) Catapult continues to build on its reputation as a key player in the development, delivery and commercialisation of cell and gene therapies, supporting sector growth. The CGT Catapult has driven developments through a range of strategic collaborations and projects in the UK and Internationally. This broad engagement enables the CGT Catapult to monitor global developments and appraise the UK from an international perspective (Annex B).

The potential of regenerative medicine to deliver very long-lasting, even curative, outcomes following a single treatment makes these therapies very different from many other drug therapies. The long-term nature of treatments and the lack of longitudinal data makes robust, evidence based, appraisal decisions on cost-effectiveness difficult. To start to tackle this problem, The National Institute for Health and Care Excellence (NICE) has completed a project to specifically examine how the current appraisal system copes with uncertainty and has made detailed consideration of possible alternative models of remuneration that may offer ways of dealing with uncertainty or lack of evidence. This study has concluded that NICE methodologies are versatile and can be adapted for these innovative treatments especially where step changes in patient's outcomes are demonstrated. In addition the report recommends the development of innovative payment models that can take into account long-term benefits to patients.

NHS England is unable to routinely commission new treatments of potential high expense in the absence of clear published evidence of benefit. Furthermore, NICE and NHS England have been exploring alternative strategies to introduce potentially costly new treatments of high patient benefit, including Commissioning through Evaluation and Managed Access Schemes. The use of this type of arrangement and willingness to consider new models of remuneration will be important in supporting the adoption of regenerative therapies in the future.

The pace at which new developments in new cellular and gene therapies are entering clinical trials continues to accelerate. The number of cell and gene therapy clinical trials continues to grow so that by May 2015 analysis by the CGT Catapult shows that there were over 50 active trials for a broad range of therapies. This expanding number of therapies and the range of applications are good evidence that the environment in the UK is becoming increasingly supportive of these therapies.

NHS Blood and Transplant (NHSBT) has developed significant experience in the handling of stem cells from their role in supporting stem cell transplantation. This means NHSBT is well-placed to facilitate the adoption of these therapies within the NHS, through providing the NHS with a unique infrastructure to support the local handling and bedside delivery of living cells. NHSBT also has established a key role in the supply of allograft materials, including skin, tendons and trachea. These allograft products may be used in a decellularised form or as scaffolds for living cells.

The RMEG review was focused on identifying the barriers that would prevent adoption in the NHS of new regenerative therapies. It is important to note that, in addition to the work directly responding to the RMEG recommendations, there are other significant initiatives that have contributed to the overall landscape for regenerative therapies. The UK Regenerative Medicine Platform (UK RMP) has created an integrated UK research strategy for regenerative therapies in the UK. The UK RMP has created five interdisciplinary and cross-institutional research Hubs, and five aligned disease focused projects. Innovate UK continues to support the focused development of enabling technologies for therapies moving towards commercialisation. The Ministry of Defence (MOD) maintains an active interest in regenerative therapies across a broad range of potential uses and may well prove to be an earlier adopter of regenerative therapies where they can support the treatment and rehabilitation of injured service personnel.

In conclusion, we consider that regenerative medicine is a successful example of coordinated Government involvement which has helped to accelerate the development of a new UK industrial sector that can deliver Health and Wealth for the UK. The overall picture for regenerative medicine in the UK is extremely positive and the pace of progress suggests that the next few years will see the clinical impact of these therapies expand rapidly (see Annex B for the UK from an international perspective).

There are still hurdles to be overcome for the commercial development of these therapies, especially in relation to the high cost of manufacture. A number of groups have been actively developing engineering solutions to reduce manufacturing costs, including the CGT Catapult and the EPSRC Centre for Innovative Manufacturing in Regenerative Medicine. These are likely to involve automation, single-use technology, and sophisticated logistics. Their success requires the continued investment in the infrastructure and training of people with the necessary technical skills.

The Regenerative Medicine CEO group will continue to advise ministers and their departments on the progress of cell and gene therapies across all sectors in the UK. However, as co-Chair, you may wish the recently established Advanced Therapies Taskforce give further consideration to some of these issues as part of its work programme.

Yours sincerely,

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Peter Thompson

Chief Executive

Human Fertilisation and Embryology Authority

Ian Trenholm

Chief Executive

NHS Blood and Transplant

Dr Ian Hudson

Chief Executive

Medicines and Healthcare Products Regulatory Agency

Alan Marriot-Smith

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The Human Tissue Authority

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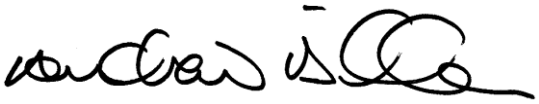

Sir Andrew Dillon

Chief Executive

NICE

Annex A – Progress against RMEG Recommendations

Annex B – The UK regenerative medicine sector from an international perspective

Annex A:

Progress with Regenerative Medicine Expert Group Recommendations

Development

1. **The Expert Group recommends that the process for consideration of funding for excess treatment costs for cell therapy trials is reviewed by NHS England, the Department of Health and the NIHR and their equivalents in the other UK countries; and that mechanisms are put in place to ensure that these costs are not a barrier to clinical trials.**

   A formal review of excess treatment costs involved in clinical trials was published in December 2015. This guidance is not fundamentally different from earlier versions but includes a specific requirement to engage with commissioners at the planning stage when undertaking costings.

2. **The Expert Group recommends the following actions:**

- **Advice about the classification and associated requirements for trials involving gene modification should be made available to researchers through the participation of Defra and the HSE in the regulatory 'one-stop shop' for regenerative medicine announced by the regulators in October 2014.**

  The 'one-stop-shop', also known as the Regulatory Advice Service for Regenerative Medicine, is hosted by the MHRA's Innovation Office and directly fields enquires that span multiple regulatory agencies including the MHRA, HRA, HTA and HFEA. In the first year this portal has dealt with 14 enquiries and a review will be published at the end of March 2016. Although not formally part of the 'one-stop-shop', links have been established to appropriate contacts in Defra and HSE but these have not yet been required to provide advice.

  In addition, the Innovation Office has received more than 270 enquiries since it was established in 2013 and approximately 20% of these are ATMP enquiries. This is in addition to other ATMP enquiries which go directly to MHRA centres and Divisions, e.g. inspectorate, licensing, Devices and NIBSC.

- **Consolidated guidance on the requirements for cell and gene therapy trials involving GMOs should be produced.**

  As in Recommendation 2 above there are established contacts between MHRA, the 'One Stop Shop' and Defra and HSE regarding issues related to GMO release for patient therapy. Consolidated guidance has not been developed but relevant guidance is available from the appropriate regulators.

- **The possibility of incorporating any additional information needed for research involving GMOs into the HRA's existing Integrated Research Application System (IRAS) should be explored.**

  Regulators at the HSE involved with GMOs have begun to investigate the possibility of integrating GMOS within the existing IRAS system.

- **Defra should examine best practice in applying GMO legislation in other EU countries, so as to ensure that UK requirements are comparable and proportionate.**

  The regulations related to GMO are covered by legislation in the form of EU Directives but these are translated by member states into national member state law in a way that allows regulators to refine implementation as required.

3. **The Expert Group recommends that unlicensed regenerative medicines should not be supplied under the Hospital Exemption Scheme where an equivalent licensed medicinal product meets the specific needs of a patient. Responsibility for deciding whether an individual patient has a special need which a licensed product cannot meet should be a matter for the clinician responsible for the patient's care.**

   The production of unlicensed ATMP's in the UK is either through the grant of a "specials" authorisation or under the Hospital Exemption scheme. "Specials" remains an important part of the manufacturing system but should not undermine manufacture on a commercial basis and to prevent this specific are conditions attached to the licences in the UK.

   Approximately 20 sites in the UK are involved in the production of 'specials' but only one site produces therapeutic products under the hospital exemption scheme. The current system appears to be operating successfully in the UK but the transposition of EU directives into national legislation is a member state responsibility and this has resulted in differences in the application of the Hospital Exemption clause across the EU. The CGT Catapult have requested European Medicines Agency (EMA) guidance on this area, in particular the definition of non-routine manufacture and have requested that the EMA recommends that Hospital Exemption should only be used where there is an unmet medical need and should not be used to supply product when there is EU licensed alternative. There remains a need to examine the existing system of exemptions to ensure that a consistent and proportionate approach is taken across the EU. This area could form part of future EU-wide policy development.

4. The Expert Group recommends that the developers of regenerative medicines give serious consideration to seeking marketing authorisation through the adaptive licensing pilot scheme where appropriate.

In March 2014 EMA launched a pilot project to explore how the adaptive pathways approach might work in the existing regulatory framework with real medicines in development. The name of the project was changed from adaptive licensing to adaptive pathways to emphasise the fact that its aim is to foster and facilitate the pathway of product development to potentially achieve earlier access to medicines through an early dialogue involving all stakeholders.

This ongoing pilot provides a framework for dialogue between stakeholders, including patient and health-technology-assessment bodies, to explore different options in a 'safe harbour' environment and consider detailed technical and scientific questions based on concrete examples. A number of ATMPs have already been submitted as candidates for the scheme.

In parallel, the Innovative Medicines Initiative (IMI) runs ADAPT-SMART, a project investigating the conceptual framework that could be used in adaptive pathways, including tools and methodologies.

Support is also available to developers through EMA's Priority Medicines (PRIME) scheme. The scheme, launched on 7 March 2016, aims to strengthen support to medicines that target an unmet medical need. Through PRIME, EMA offers early, proactive and enhanced support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicine applications. This will help patients to benefit as early as possible from therapies that may significantly improve their quality of life.

The ongoing development of PRIME and adaptive pathways will be supported by the European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP). The main objective of the STAMP Expert Group is to assist the Commission services to identify ways to further improve safe and timely access and availability of medicines for patients, including specific categories of medicines (e.g. orphan medicinal products, antibiotics etc.) or medicines for specific therapeutic areas.

5. The Expert Group recommends that the UK, through the relevant MHRA Competent Authorities, encourages the EMA to explore options to improve accessibility, including the extension of the certification procedure, to academic groups and not-for-profit organisations.

CGT Catapult, as an independent body and as part of the Alliance for Regenerative Medicine, have met with the EMA and the European Commission to discuss the possibility of extending the certification scheme, as set out in the provisions for SMEs in EC regulation 726/2004, to include academic and other not-for-profit groups. Both organisations are investigating this possibility.

6. The Expert Group recommends that the UK, through the MHRA Competent Authorities, uses this opportunity to press for EU-wide consensus on the following:

- **The removal of any disparity in categorisation across the Member States for products which straddle the boundary between cellular therapies regulated under the EU Blood Directive (EUBD) and the EU Tissues and Cells Directive (EUTCD) and cellular therapies which are medicinal products and regulated under the ATMP Regulation. Consideration should also be given to European classification coordination by the EMA's Committee for Advanced Therapies (CAT) to be subsequently adopted by all Member States.**

  The transposition of directives into national legislation and practical application is a member state responsibility. The European Commission are examining the crossover of EUBD and EUTCD and their interplay with the ATMP Regulation, but a reopening of the ATMP regulation is not thought desirable by the industry. In the meantime the MHRA and HTA have issued a Policy statement on the Regulation of Blood as a Starting Material for ATMP Manufacture [1] which permits blood collected for this use to be procured under either a Blood or Tissue establishment Authorisation and which is supported in principle by the Commission's view at a recent Tissues and Cells[2] Competent Authority meeting.

- **Broadening the scope of the quality and non-clinical data certification scheme, when the ATMP Regulations are reviewed, to all types of applicants.**

  See response to recommendation 5.

- **A review of the cost structure both for scientific advice and to assist with the affordability of ongoing regulatory fees.**

  The incentives offered to SMEs by the EMA include reduced administrative and procedure costs, this includes reductions in scientific advice meeting costs and some post-marketing maintenance fees. Since these are laid down in the provisions for SMEs in EC regulation 726/2004 they cannot be extended to non SMEs under this provision. CGT Catapult and other industry members have requested that similar incentives be extended to non-for-profit organisations.

  It is worth noting that affordable scientific advice can be obtained from NICE[3] and MHRA[4] either independently or on a joint basis. In addition NICE has also run joint Scientific Advice Seminars as described in response to recommendation 15.

[1] HTA and MHRA Policy on the Regulation of Blood as a Starting Material for ATMP Manufacture
[2] http://ec.europa.eu/health/blood_tissues_organs/docs/ev_20151203_mi_en.pdf item 2.3.1
[3] https://www.nice.org.uk/about/what-we-do/scientific-advice/nice-mhra-scientific-advice
[4] https://www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra

- **The development of a risk- based model for point of care devices and/or relatively simple preparation steps and a guideline for comparability assessment detailing quality control and validation requirements and suggesting solutions utilising practical case studies.**

  The MHRA is actively involved with the Commission, EMA and a group of Member States on a review of GMP guidelines for ATMPs which includes the use of point of care devices for manufacture (see also Recommendation 17). MHRA, in association with CGT Catapult, continues to work on issues of comparability and proportionate regulatory requirements at EU level.

7. The Expert Group recommends that this issue of product comparability across multiple manufacturing sites be considered by developers, early in the development programme of a regenerative medicine, seeking advice when necessary from the appropriate regulator.

The Pluripotent Stem Cell Platform[5] has held a workshop on comparability and a paper will be published. CGT Catapult are working with academic groups, including Loughborough University, to develop a model to investigate the issues associated with comparability across multiple manufacturing sites (distributed manufacture). In addition CGT Catapult are working with the MHRA on a position paper on the issues associated with a distributed manufacturing model with a view to this going to the EMA for consideration.

8. The Expert Group recommends that extra efforts be made to communicate the current Competent Authority position on blood components as starting materials for ATMPs.

As stated above in relation to recommendation 6, the MHRA and HTA have worked together to develop and publish a position statement on the use of blood as starting materials for cell therapy medicinal products. The European Commission have issued a statement that supports this approach.

9. The Expert Group also recommends that, given the existing network of appropriately regulated centres with Tissues and Cells licences broadly aligned with ATMP developers, the UK should press for a consistent approach throughout the EU allowing the use of centres with Tissues and Cells licences to procure and conduct mandatory

[5] The Pluripotent Stem Cell Platform (PSCP) is a translational alliance, involving Sheffield Centre for Stem Cell Biology, the WT/MRC Stem Cell Institute, Cambridge University Health Partners, the Loughborough led EPSRC Centre for Innovative Manufacturing in Regenerative Medicine, the Wellcome Trust Sanger Institute, the Babraham Institute and NIBSC.

tests on blood components that are to be used as starting materials for ATMP development.

As stated above in relation to recommendations 6 and 8 the MHRA and HTA have introduced flexibility and agreement at an EU level will promote this flexibility with the other national Competent Authorities.

10. The Expert Group recommends that the format and use of the Cell History File is proposed by the MHRA as an EU-wide template.

The MHRA and CGT Catapult finalised the Cell History File template for developers and this has been published on the CGT Catapult website. The concept and template has been welcomed by developers both in the UK and internationally.

11. The Expert Group recommends that consideration is given to how potential opportunities provided by the UK Stem Cell Bank and the Cord Blood Bank might be utilised as future base material for the development of allogeneic products.

NHSBT has applied for Biobank status for its Cord Blood Bank and this application is ongoing. This would allow lower-grade cords that are ultimately unsuitable for transplantation to be used for research purposes.

12. The Expert Group endorses the proposal that NICE should consider the findings from one or more 'mock' technology appraisals and whether changes to its methods and/or processes are required. Any appraisal should include expert advice.

NICE has completed and published a detailed study exploring the assessment and appraisal of regenerative medicines that has included review of the appraisal process for a hypothetical regenerative medicine product. The project involves the analysis of a series of scenarios that explore how the appraisal process is affected by various levels of uncertainty. An additional part of the project is a consideration of possible alternative models of remuneration that may offer ways of dealing with uncertainty or lack of evidence. The study was published on 29 March 2016.

13. The Expert Group recommends that an innovative business model is developed between industry, government and the NHS, to support the early adoption of regenerative medicines in the NHS.

NHS England has established a new directorate within Specialised Commissioning with a commercial focus. This directorate has worked on a number of innovative business models. The most established is commissioning through evaluation but recent approaches have included the creation of

Managed Access Schemes in collaboration with NICE. The directorate includes a commercial negotiating team and this team are exploring a range of approaches that include an element of risk-sharing.

14. Given the specialist nature of regenerative medicine the Expert Group recommends that NHS England's cross-CRG for regenerative medicine be maintained; and, potentially, further developed into a formal 'CRG for regenerative medicine' as new products are identified for consideration. This CRG should include clinicians covering an appropriate range of specialties and experiences in regenerative medicine in order to provide more specific expertise, insight and advice to other CRGs. The other UK health departments should also consider comparable arrangements.

NHS England has been reviewing the organisation of Clinical Reference Groups (CRGs) and the total number of groups is likely to be rationalised from the current 68 to around 42. In the absence of specific regenerative medicine CRG it may be possible to highlight new and innovative technologies to the commissioning teams with the use of stakeholder surgeries. These surgeries allow groups, typically SMEs to introduce new technologies that may have important implications for service delivery.

15. The Expert Group recommends that NICE develops a scientific advice product, focused on the needs of SMEs developing regenerative medicines, and explores options for supporting access to this. Additionally NICE and NHS England, together with the Cell Therapy Catapult, should jointly develop and provide a bespoke seminar on evaluation methods and on how best to develop a value proposition for regenerative medicines.

NICE has opened an Office for Market Access (OMA) to give commercial stakeholders access to a dedicated team at NICE that they can approach for enquiries relating to health technology evaluation and market access issues. OMA has already had approaches from several companies developing regenerative medicines. In addition NICE Scientific Advice has developed and delivered a seminar involving the CGT Catapult, MHRA and NHS England providing guidance on the evaluation process for companies. Feedback from the first seminar was very positive and the event will be repeated in April.

The exploratory study of the appraisal of exemplar regenerative medicine products in response to recommendation 12 is also relevant. This study was commissioned by NICE to highlight key issues in the evaluation of regenerative medicines and explore alternative models of remuneration.

Embedding regenerative medicines in mainstream NHS services

16. The Expert Group recommends that the Department for Business, Innovation and Skills and the Department of Health engage with NHS England and other relevant partners, including the Cell Therapy Catapult, to further develop the concept of Cell Therapy Centres of Excellence and how they should be identified, and examine the options for their coordinated, collaborative development.

NHS England and CGT Catapult are continuing to work together to improve the delivery of cell therapies to patients. At present NHS England does not have plans to formally define Centres of Excellence.

17. The Expert Group recommends that regulators review the requirements placed on final preparation and/or finishing of regenerative medicines when intended for immediate administration and the requirement for low risk manufacture to be carried out in GMP facilities. This should also take into account the role of hospital pharmacies and, in particular, how governance oversight may be most appropriately exercised over existing arrangements for blood banks, haematopoietic stem cell processing and cell therapy manufacturing facilities.

As in bullet 4 of Recommendation 6, the MHRA is actively involved in a review of GMP guidance at EU level which is working to highlight the existing flexibilities in GMP and to provide further guidance as required. MHRA's position is that the level of regulation must be proportionate to the level of risk based on the principles of quality risk management.

18. The Expert Group recommends that the UK blood and tissue services, in partnership with the Cell Therapy Catapult and other stakeholders, including industry, undertake analyses of existing infrastructure to assess the options for the delivery of a cell therapy procurement, manipulation, storage and distribution network. This should be informed by the outputs from the Cell Therapy Catapult's Seamless Freight Initiative, building upon the existing Blood Service competencies in this area and support the development of Cell Therapy Centres of Excellence.

CGT Catapult have extended their annual analysis of UK GMP licensed manufacturing facilities to include gene as well as cell therapy capable sites. This includes facilities within the Blood Services; within the hospital setting; and commercial supply companies.

Follow-on workshops are planned, to map further the Blood Service capabilities onto this framework and further define industry and clinical requirements. Logistical and clinical experience shall be evaluated, including data from the EU supply chain test bed system, currently being set up by CGT Catapult as part of the Seamless Freight platform.

In parallel, NHSBT has worked with the CGT Catapult to determine how its cell therapy infrastructure could be utilised to support the logistical aspects (i.e. movement, manipulation, final preparation and storage) of various types of cell therapy products from their site of origin to UK hospitals.

19. The Expert Group recommends that an education and training programme for cell therapy should be designed, commissioned and rolled out across the appropriate NHS workforce.

NHSBT has developed training manuals for the British Blood Transfusion Society and the British Association of Tissue Banking, which support a "Specialist Certificate" qualification in Cell and Tissue Sciences. This programme is currently being updated, but is available for use outside NHSBT. NHSBT has also developed an internal training manual for its Cellular and Molecular Transplantation division.

It is possible if there is sufficient demand, it may be possible for NHSBT to develop a Higher Specialist Scientific Training course (i.e. for consultant clinical scientists) in cellular therapies. This would need support from the Royal College of Pathologists and the National School for Healthcare Sciences as well as various stakeholders such as the BIA. NHSBT has previously prepared this type of programme for Clinical and Laboratory Transfusion, but would require additional resource to undertake this work on a UK-wide basis.

20. The Expert Group endorses the development of the NICE/NHS England observational data unit and its application to the collection of data on regenerative medicine products. The Expert Group also recommends that the Department of Health ensures that appropriate arrangements are in place for the very long-term follow-up of patients receiving regenerative medicines.

Where data collection is required for the commissioning through evaluation this is currently contracted to NICE. It is possible that a similar arrangement could apply for regenerative therapies although this would need to take account of the open-ended nature of the data collection. Long-term data collection and follow-up will also be important to support innovative models of remuneration based on long-term clinical results.

Going forward, remaining engaged

21. The Expert Group recommends the establishment of a Ministerial Group, similar to the Ministerial Medical Technology Strategy Group and Ministerial Industry Strategy Group, for regenerative medicine.

At the suggestion from the Minister a high level group involving the Chief Executives from the key delivery organisations was created as a specific way to

monitor progress and drive the delivery of the recommendations in the report. The Advanced Therapies Taskforce will provide scope to cement the progress made and define future priority areas.

Annex B

The UK regenerative medicine sector from an international perspective

Whilst historically people have talked about Regenerative Medicine, Cell Therapy, Gene Therapy and Tissue Engineering as quite separate and distinct areas. Many of them are classed by the regulators as "Advanced Therapy Medicinal Products" (ATMPs) with often similar characteristics and issues. With overlapping and accelerating technology blurring distinctions, most commentators use the terms Advanced Therapy or Cell and Gene Therapy to cover all the specialisms, wrapping in regenerative medicine and including some therapies that are not regulated as ATMPs. The technology overlap is best exemplified by the dramatic rise of Gene Modified Immune Cell therapies where cells are modified ex vivo using viral vector technology and with the advent of Gene editing technologies further impacts are likely across the whole sector.

1. The Cell and Gene Therapy Catapult: establishment and early impacts

Since its inception in 2012, a number of fundamental barriers to the growth of the industry have been removed or lowered and a significant national asset has been developed in the form of the Cell and Gene Therapy (CGT) Catapult. Over the last year, the CGT Catapult invested £15.6m in the UK, including £2.4m of third party funding, materially meeting both its key performance indicators and milestone targets. Over the last three years, the CGT Catapult has invested £21.3m of funding into projects and leveraged a further £27.3m of third party funding into businesses and projects.

Key additions to the CGT Catapult assets in 2015/16 include substantial advancement of the £55m manufacturing centre at Stevenage towards seeding a global manufacturing cluster, and the development of a new viral vector industrialisation capability to meet the immediate needs of the gene therapy industry.

In a short space of time, the CGT Catapult has developed an impressive list of successful outputs, such as; two spin outs of immuno-oncology companies; assisting academic groups onto a path to commercialisation of their technologies; working with a UK company to develop much needed medical devices which will be manufactured in the UK; actively shaping the environment for cell and gene therapy; and positioning the new manufacturing centre as part of the global infrastructure.

From these, and other outputs, have evolved a series of outcomes which generate economic growth, including; ReNeuron raising over £100m of investment; Athersys Inc. choosing the UK as a base for a European clinical trial and establishing an affiliate here; TxCell contracting the CGT Catapult for its process development; and Asterias Biotherapeutic creating a UK subsidiary and contracting the CGT Catapult for its essential process development.

2. Investment

According to the Alliance for Regenerative Medicine, by the end of 2015 there were a total of over 672 companies working in cellular, gene and other regenerative medicine breakthroughs. Whilst North America dominates with 349 companies, 185 are established in Europe, most of the balance being in Asia. According to the Cell and Gene Therapy Catapult the number of UK companies has grown by over 35% since 2012 and now stands at over 40. Half of the companies are expanding R&D and manufacturing with corresponding increases in recruitment. 2017 is expected to be marked with the first sales of high value genetically modified cellular immune oncology products with Novartis leading the pack. Nine new UK cell and gene therapy companies have been formed in the last 12 months alone with the UK often acknowledged as the leading country in Europe. The UK is home to several companies that have been developing immunotherapy products for some time and as new technologies have been developed several more have been formed, a platform from which the industry can grow rapidly. Investor perceptions of the gene modified immune area are strong, with the extension of this investor interest to "in vivo" gene therapies and genome editing.

2015 has been a standout year with $10.8bn of financing raised globally, mostly in the first part of the year representing an increase of 106% compared to 2014. Adaptimmune Therapeutics Plc, an Oxford based biotech, successfully closed a $191 million IPO, followed by Celyad, REGENXBIO, Kiadis Pharma and Benitec Biopharma who all closed successful IPOs. However in the latter half of 2015 public markets all but closed to biotech IPOs as investors perceived the biotech industry as being overvalued combined with other uncertainties raised during the US presidential candidate campaigns. It is still not yet clear how this slow-down in public financing will impact the private markets. Much of this activity remains focused in North America.

In the engineered T-cell sector active UK companies include Adaptimmune Therapeutics Plc, Leucid Bio, Autolus, ImmunarT, Cell and Gene Therapy Catapult TCR and Oxford BioMedica. There remains significant potential to grow UK companies in the immune therapy sector and advance other sectors toward the same levels of interest. Whilst it is unclear how private investment will be affected as a result of the tight public markets, funding from a few sources has been quite strong. As recently as early March 2016, UK Car-T company Autolus, a UCL spin out initially funded by Syncona, raised a £40m series A investment from Neil Woodford's patient capital fund.

3. Market Size and the expansion of in vivo gene therapy

In contrast to 2012 when the Cell and Gene Therapy Catapult was launched, companies, such as GSK, are now quoting cell and gene therapy as the next pillar in their healthcare offering and the source of future growth and

profitability. Cell and gene therapy market forecasts range from $67bn per annum by 2020 for the industry as a whole to $10bn by 2025 for individual classes such as Gene Modified Immune Therapies or Ex-vivo Gene Therapies.

The industry is expected to exceed that of the global biologics segment (circa$75bn pa), with gene modified therapies leading the way. Novartis, Juno and Kite, all initially US focused, are expected to bring their cancer gene therapies to market as early as 2017, with predictions of peak sales exceeding 100,000 patients and reimbursement prices as high as $500,000 per treatment or more (a cost comparable to the upper end of hematopoietic stem cell bone marrow transplants today).

There has also been a major increase in the growth of new and ongoing clinical trials for innovative in vivo gene therapies, particularly those using adeno-associated viruses (AAV) to deliver modified genes to cells for the treatment of haemophilia or retinal therapy. Based on recent German state level pricing approval for Glybera (€1.1 million) (an AAV based in vivo gene therapy delivering the lipoprotein lipase gene intra-muscularly), the global in vivo gene therapy industry can possibly turn into a $500 million industry as early as 2020.

Transactions over the period by Roche ($0.5Bn deal with SQZ Biotech), Celgene ($1Bn for a ten year partnership to access Juno Therapeutics pipeline of CAR-T drugs) and AstraZeneca ($1Bn invested in immuno-oncology deals in 2015) combining its checkpoint inhibitor with Juno's CAR-T in non-Hodgkin's lymphoma are key indicators of the renewed commercial interest in engineered immune cell therapy. This growth will undoubtedly have knock-on benefits across the supply chain, for instance it is likely to create a booming market for bioreactor equipment attracting equipment manufacturers currently working with biologics therapy developers to enter the market, and UK companies such as TAP Biosystems Limited (Sartorius) and Algaris Cell Limited are developing innovative bioreactors to support this sector.

During the year we have also seen significant investor focus in "in vivo" gene therapies and genome editing technologies, with Florida based AGTC signing a $1.1Bn collaboration with Biogen involving its AAV-based gene therapies for the treatment of rare eye diseases -Cas9 genome editing company CRISPR Therapeutics raising $89 million in series A and B financing from venture capitalists and strategic investors SR One and Celgene Corporation.

4. Summary

Overall there is increasing activity by investors of all types, from institutional and pharma fund managers to corporate venture funds, venture capitalists and angels, who are all carefully monitoring new advances as the field gains ground and credibility. This increased corporate and financial investor appetite in cell and gene therapy provides the opportunity and demand for the CGT Catapult. However, financial challenges continue in other cell therapy technologies as often the clinical efficacy is still to be demonstrated. Far from making the technical problems go away the investment makes solving the technical problems much more acute and hence sharpens the role of CGT Catapult. The

CGT Catapult will maintain an active role de-risking and developing these technologies for potential investors as well as working to ensure the UK captures investment in gene modified immune therapies. The UK has established itself as the key place in Europe for Advanced Therapy translation; progressing therapies through clinical trial, manufacturing and adoption by the NHS will cement that position.