Regenerative Medicine Regulatory Workshop

MHRA, London, 30th October 2012

The Academy of Medical Sciences

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Contents

Summary of Key Messages

- There is considerable flexibility in the UK regulatory framework to accommodate regenerative medicine. Nonetheless, further harmonisation of guidance from the regulators and advisory bodies would be helpful to the field.

- A review of the nature of preclinical data required for cell-based therapies was considered valuable. New models and approaches may be needed to assess the pre-clinical and clinical safety, quality and efficacy of this novel class of therapies.

- Ease of flow through from research and development to commercialisation:

    - Accelerated routes to the patient (hospital exemption and specials schemes) are very useful in making these disruptive technologies available, and experience gained can be used in formal development. However, clarification across Europe of their eligible use is needed. This would be helpful in striking an appropriate balance between commercial incentivization and non-commercial and next generation development.

    - Participants commented that reimbursement is a major issue and help at all stages is needed. Early and progressive reimbursement would be a huge advantage. While regulatory approval is through the European Medicines Agency and is EU-wide, reimbursement decisions are made state by state; hence a clear route map for reimbursement would be useful.

- Opening up the full potential of the NHS to accelerate clinical trials, access to patients, product development, and to support the development of appropriate health economic models to inform approaches to reimbursement of regenerative medicine products, would greatly help the field to progress and provide a significant competitive advantage to the UK.

- Social science research has shown the importance of *institutional readiness* within the health care system, which is needed to complement technological readiness. This will critically depend on several factors - the NHS evaluating regenerative medicine products against comparator approaches, cost consequence analysis, the impact it might have on patient pathways, and wider workflow in the NHS setting.

- It is important that, with the dissolution of the Gene Therapy Advisory Committee, appropriate scientific expertise can still be accessed for the review of these products. It will be important that the new assessment structures, which could helpfully provide a clearer demarcation of responsibilities, ensure appropriate and timely expert scrutiny of relevant proposed trials.

- In light of the field's discrete aspects, participants stated that it would be worth considering a national commissioning agency for regenerative medicine.

1. Workshop Introduction

1.1 Martin Wilkins (Imperial College London)

- A forum to consider regulatory lessons and challenges from emerging cell-based therapies was proposed by the Ministerial Industry Strategy Group (MISG), an Association of the British Pharmaceutical Industry (ABPI) and Medicines and Healthcare products Regulatory Agency (MHRA) group chaired by Sir Alastair Breckenridge. The idea resonated with the Academy of Medical Sciences (AMS) and similar plans emerging through the Medical Research Council (MRC) and the Economic and Social Research Council (ESRC) and quickly won support for a joint workshop. This workshop was held at the MHRA in London on 30th October 2012 with sponsorship from AMS, ABPI, ESRC, MRC and MHRA. The attendees are listed in Annex I.

- The specific aims of the workshop were to understand:
  - the current regulatory environment in the UK/Europe and identify it's suitability for the current R&D needs for cell-based regenerative medicine;
  - the key areas of regulatory uncertainty and concern regarding the development of cell-based regenerative therapies; and
  - the likely needs for the area regarding future scientific progress.

- The workshop was designed around the following outputs: (a) a meeting report to be publically available through the websites of participating sponsors, and which would inform further work, e.g. an international meeting that MRC is proposing to host with the California Institute of Regenerative Medicine and the on-going House of Lords Select Committee on Regenerative Medicine; and (b) an update of the Stem Cell Tool kit to include other aspects of regenerative medicine through the inclusion of a series of case studies, to help people develop and translate their science.

- While the workshop was hosted by the sponsor group, the views expressed in this report represent those of the workshop participants, as collated over the course of the meeting, and do not necessarily reflect those of the sponsors.

1.2 Regulatory Overview – The Current Position

Elaine Godfrey (MHRA), Imogen Swann (Human Tissue Authority)

- Advanced Therapeutic Medical Products (ATMPs) fall both within the Human Tissue Authority (HTA) and MHRA. The sourcing of tissues and cells for ATMP falls under HTA, while trials, including Good Manufacturing Practice (GMP), fall under MHRA. The two agencies work closely together to provide joined-up regulation with joint inspections.

- Two key questions need to be addressed when developing a product for regenerative medicine

  - Will the product be classified as a medicine?
  - If yes, then will there be a clinical trial with a view to marketing authorization or will it be used via the specials scheme?

- All clinical trials come under the clinical trials directive as transposed into UK law, which was amended to capture tissue engineered products. The Commission has published its proposals for a new clinical trials regulation to replace the Clinical Trials Directive but this draft does not propose a substantive difference to the regulation of regenerative medical products.

- Clinical trials are a national competence. Market Authorization is at EU level. Undertaking a trial in multiple member states requires approval for the trial from each state. There is no pan-EU approval

process for trials. Regulators are looking to build on harmonization to streamline parallel approvals but are not looking to develop a single approval approach.

- There is an opportunity via the voluntary harmonised procedure introduced by the clinical trials facilitation group to have a single scientific assessment process with a single set of questions. If addressed appropriately it provides an approvable status for the science, followed by a quick administrative step in each country. This approach is open to both commercial and academic groups. There is a risk for small groups that this process can lead to a long list of questions to address, which can be tricky to do in the short time provided.

- The UK has the hospital exemption scheme which sits alongside the 'specials' provisions. The test for hospital exemption is that it is a non-routine manufacture, and for specials it is an unmet clinical need. Hospitals exemption is restricted to one member state. With 'specials' it is permissible to import/export to another EU member state as long as approval for importation is in place.

- The regulatory authorities encourage discussion with investigators at the early stage of development. They operate to provide free advice at national and EU level. The objective is to protect patients in clinical trials without holding up clinical research.

Gopalan Narayanan (MHRA and member of the European Medicines Agency Committee for Advanced Therapies)

- To date there have been nine applications to the European Medicines Agency (EMA) for product licensing, a lower number than expected. Five of these were for cell-based products, the other four for gene therapy. Two applications have received positive approval. One of these is a tissue engineered product – Chondrocelect® for cartilage regeneration in the knee. The other is a gene therapy - Glybera® for the treatment of lipoprotein lipase deficiency.

- Somatic cell therapy and tissue engineered products are defined differently, but the regulatory requirements have minimal differences. Early engagement with the EMA to determine whether a product will be classified as an ATMP is open to both academics and commercial groups. It is free, and not mandatory but helps with subsequent engagement with regulators.

- Certification of an ATMP is a specific procedure only available for small to medium sized enterprises (SMEs), not academics. It is possible to obtain an opinion from the EMA's Committee on Advanced Therapies on whether the quality, and where available non-clinical data, are acceptable in terms of regulatory compliance and scientific robustness at a very early stage of development. It is envisaged that the Committee's response could help the SME engage with larger companies or venture capitalists. It is not a preauthorisation for clinical trials, but could help firms to develop products. Uptake has been disappointingly low. The two requests for an opinion submitted to date have both gone on to receive certification. In discussions, industrial participants suggested that the low uptake might be due to the benefits of certification not being clear.

- The EMA provides scientific advice to academic and commercial groups on any combination of quality, non-clinical and clinical issues.

1.3 Overview of the Therapeutic Pipeline in Cell-Based Regenerative Medicine

Rob Buckle (MRC) and Mark Lowden (University College London)

- The UK and Germany are at the forefront of research in regenerative medicines in the EU.

- Looking further afield, international competition is intense. Heavy investment in the field is being made in North America and the Far East, and in the latter case South Korea has now approved eighteen ATMPs (against two in the EU).

- A review of UK spend per Technology Readiness Level (TRL) showed that the majority of the combined Research Council and Technology Strategy Board funding is focused on the earliest TRLs with levels reducing as projects move further down the development path, reflecting the relative immaturity of the field.

- A 2013 MRC survey of UK regenerative medicine research activity, spanning cell-based approaches and gene therapy with a stem cell basis (but excluding drug based regenerative medicine studies), showed:

  - 61 products in development, of which 80% are academic, 20% are commercial.
  - 15% studies are using human embryonic stem cells (hESC), 85% are using adult stem/progenitor cells. There are currently no induced pluripotent stem cell (iPSC)-based therapies under development.
  - 50% autologous cells, 33% allogeneic cells, with 17% not specified.
  - With respect to stage of development, 43 of the studies are preclinical, and 18 are in Phase I/II.
  - The most common therapeutic areas are musculoskeletal (26%) and eye (20%) diseases, followed by liver (12%), cardiovascular (10%) and neurological (10%) diseases.

- By way of comparison, a top-level analysis of the portfolio of late-stage translational studies funded by the Californian Institute of Regenerative Medicine (CIRM) indicated a number of similarities regarding areas of clinical focus. However, it was noted that CIRM's therapeutic pipeline included one iPSC-based product, while there was almost no research in the musculoskeletal area. The lack of musculoskeletal research supported by CIRM may reflect the significant investments made at sites such as the Wake Forrest Institute of Regenerative Medicine by the National Institutes of Health, the Department of Defence and others.

1.4 Socio-Economic and Policy Perspective

Chaired by Andrew Webster (University of York): with Alex Faulkner (University of Sussex), Sue Simpson (NIHR Horizon Scanning Centre), James Mittra (University of Edinburgh)

- Making goods measureable and comparable is a driver of new market creation, but in the regenerative medicine field there is considerable uncertainty regarding data and product classifications, both in the UK and internationally. This means there is a very strong need for soft interactions between the regulators and stakeholders, especially with MHRA on the one hand, and NICE and Health Technology Assessment agencies on the other, because their approaches to the central issue of product classification and scientific evaluation are very different.

- Similarly, a key intermediary agency for the NHS, the NIHR Horizon Scanning Centre, which provides notice of significant new and emerging health technologies up to three years prior to their launch in the NHS, does not have experience of how long it will take for various types of regenerative medicine therapies to diffuse since the product and development models are very different from drugs and devices. In response they have undertaken horizon scanning reviews to identify developments in cardiovascular disease, ophthalmology, neurological conditions, musculoskeletal disorders and skin conditions/wounds. They have also prepared detailed briefing reports on two current products that are closer to market.

- Overall, from a corporate perspective, research by the panel members shows that the most important factors are future regulatory and reimbursement systems, future market position/competitive landscape, future costs of inputs to manufacture process, requirement for developments in cryopreservation and GMP solutions. Companies producing starting materials have a better understanding of regulatory pathways/risk than therapy companies entering the field, as they already understand much of the regulatory framework.

2. Case-Studies of Current Early Phase Trials

Chaired by Paul Kemp (Intercytex): with John Sinden (Reneuron), Maria Pascual (Tigenix), Eleanor Berrie (University of Oxford)

- Industry has developed and matured in terms of tools, technologies and business models and gained a lot of experience in developing stem and non-stem cell therapies both nationally and internationally.

- 85% of industry activity in regenerative medicine is focused on orphan indications.

- Regulatory agencies have been generally very helpful. However, SMEs and the academic community would welcome further guidance and a route map setting out the regulatory pathway from first in man clinical trials (CTs) to Marketing Authorisation Application (MAA), spanning both UK and EU regulators, clearly showing touch points between MHRA and EMA. Consistency of advice on CTs and MAAs would be helpful.

- Non-dilutive grant assistance for clinical studies was acknowledged as very helpful.

- There is a lack of Regulatory consultants and GMP Qualified Persons with ATMP experience to service industry.

- The magnitude of HTA's £11,000 a year licensing fee was highlighted as an issue.

- Some of the "mechanics" of the application process for regulatory approval was raised as an issue (e.g. the need to send documents by mail and CD-ROM rather than by email).

- There was general agreement that, in most cases, pre-clinical animal models are of little relevance to cell therapy.

- There are no approved devices for the delivery of cellular therapies. Therapy developers have to develop and get approval for delivery devices under the Medical Devices Directive in parallel with therapy development. Simplified regulatory approach for cells together with medical devices would be helpful.

- The ability to approach patients ahead of a trial, to canvas their level of interest, would help ensure that recruitment targets are realistic.

- Due to the nature of cell therapies, for example stability and shelf-life, they will likely require regional manufacture. If this is the case, the lack of harmonization of regulation across regions such as the US, EU and Japan could be a significant barrier to commercialization.

- The NHS is not seen as an early adopter of innovation and help here to leverage their potential would have a big impact on UK industry.

3. Innovative Therapies under Development

Chaired by Anthony Hollander (University of Bristol) and Robin Ali (University College London): with Siddharthan Chandran (University of Edinburgh), Julie Daniels (University College London), Mark Lowdell (University College London), Stuart Forbes (University of Edinburgh), Paul Whiting (Neusentis), Ludovic Vallier (University of Cambridge), Andrew Baker (University of Glasgow).

- Broadly speaking, cell-based therapies can be categorised according to the extent of cell manipulation involved during manufacture: minimally manipulated (essentially where cells are taken,

perhaps enriched and used), somatic cell therapies (where cells undergo culture prior to use) and pluripotent cells (human embryonic or induced pluripotent cells).

- Typically cell-based therapies: (i) are designed to address rare conditions; (ii) are led by academic centres; (iii) and are dominated by proof-of-concept studies, with uncertain commercial prospects.

- Protocols involving cell differentiation can be lengthy and complex. Turning research production into well-defined GMP protocols is a challenge. In addition to sourcing GMP grade starting materials, there are the additional hurdles of developing and validating Quality Control and release assays, which are costly undertakings.

- This raises the question of the extent to which existing regulation is applicable to cell-based therapies and whether all cell-based therapies should be treated the same. For example, should the requirements for 'personalised manufacture' (i.e. single batches for a specific patient) be the same as for commercial manufacture? Extending this to an extreme example, how should we manage a personalized induced pluripotent stem cell line and should this be comparable to characterization of embryonic stem cells to be used for potentially thousands of people.

- While the science is advanced, it is not at the stage where large numbers of credible phase II studies can occur. Mechanisms of action are usually only poorly understood. There is a particular problem with the modelling of chronic neurological disease in animal models, which is a very difficult challenge. Furthermore, most neurological diseases are multi-focal. It will only be possible to get proof of concept with a focused approach, but clinical impact will usually require a more distributed delivery system. For example, whilst a targeted delivery approach could work in stroke and Parkinson', because of the localised nature of the degeneration, for all other major neurological diseases (e.g. Alzheimer's, other dementias, Multiple Sclerosis), which are multifocal, there is a question of how cells can be delivered to the multiple sites at which regeneration must take place.

- We have not yet solved the problem of dosing in regulated studies. In pharmaceutical development, dosage is a key issue. But we have a major problem in cell therapies because if we extrapolate directly from animal models in terms of cell dose/kg the required cell numbers would probably be lethal. Therefore we need to undertake careful dose escalation studies in humans rather than animals and we must also be aware that with chronic disorders the dose requirement will change over time, i.e. a patient with Alzheimer's today will have to have a higher dosage in a few years. This problem highlights the need for ethically justifiable experimental medicine.

- There is a good deal of duplication in the regulatory path. Having a coordinated hub/integrated regulator that could help navigate this landscape would be very helpful, as it would ensure that more studies are undertaken in a smart way and would replace the current reliance on websites, flow diagrams and acronyms that must be interpreted by the user.

- It is difficult to design clinical trials for cell therapies. Ideally this requires placebo (or 'sham') surgery and high enough statistical power to make a convincing scientific case. Furthermore, for most therapeutic areas there are only poor outcome measures that can be used in clinical trials. Therefore better methods to measure efficacy and other outcome metrics are badly needed. It follows that more investment is required for the underlying basic science but investment is also needed to develop the clinical science infrastructure, to ensure an understanding of how it will work and to develop novel trial designs.

4. Summation

Chaired by Martin Wilkins (Imperial College London)

- The MHRA believe that there is a lot of flexibility in the existing regulatory framework. This includes hospital exemptions in recognition of the clinical need for hospital-based treatments where there is no prospect of commercialisation or where it might inform the development of future treatments.

- Given that many cell-based studies originate from academia, there is a need for better support for academics in navigating regulatory requirements. The Cell Therapy Catapult will offer such advice and guidance. The Gene Therapy Advisory Committee, before its dissolution, offered both scientific and regulatory advice, and had developed a body of expertise that was valuable for complex studies. With its dissolution, it is important not to lose the expertise that supports this type of study. A route map that outlines a streamlined process would help not only academics but enable commercial groups to engage in developing therapies in the UK.

- A review of the preclinical data required for cell-based therapies was considered valuable. There was concern over the quality/usefulness of many of the preclinical animal studies. There need to be improvements in exploring mechanisms of action or dose.

- Positive outcome data is not collected by regulatory agencies for unlicensed medicines. This can act as an impediment to the development of licensed products based on interventions initially provided under hospital and specials exemptions.
- There is a perception and experience of EU countries (and so authorities) varying in their approach to regulating cell-based therapies. Harmonization could be helpful, as long as it did not impose undue restrictions on the field.

- Patient input and support is important. As in all emerging areas of science, it is vitally important that patients clearly understand the risks and benefits of cell based therapies.

Annex I: Workshop Delegates[1]

Prof	Robin	Ali	University College London
Prof	Andrew	Baker	University of Glasgow
Dr	Eleanor	Berrie	Clinical BioManufactuirng Facility
Prof Sir	Alasdair	Breckenridge	Medicines and Healthcare products Regulatory Agency
Mr	Phillip	Brown	Association of British Healthcare Industries
Dr	Rob	Buckle	Medical Research Council
Prof	Siddharthan	Chandran	University of Edinburgh
Prof	Giulio	Cossu	University College London
Mr	Andrew	Court	Association of the British Pharmaceutical Industry
Prof	Julie	Daniels	University College London
Dr	Phil	Driver	University of Cambridge
Prof	Stephen	Dunnett	Cardiff University
Dr	Alex	Faulkner	King's College London
Prof	Stuart	Forbes	MRC Centre for Regenerative Medicine
Dr	Elaine	Godfrey	Medicines and Healthcare products Regulatory Agency
Mr	Emyr	Harries	Department of Health
Mr	Julian	Hitchcock	Lawford Davies Denoon
Prof	Anthony	Hollander	University of Bristol
Dr	Anthony	Holmes	NC3RS
Dr	Ian	Hudson	Medicines and Healthcare products Regulatory Agency
Dr	Charles	Hunt	U.K. Stem Cell Bank
Dr	Paul	Kemp	Intercytex
Dr	Louise	Leong	Association of the British Pharmaceutical Industry
Dr	Mark	Lowdell	University College London
Prof	Chris	Mason	University College London
Ms	Rachel	Maze	House of Lords Science and Technology Committee
Dr	Mary	Mcleroy	Charles River Laboratories
Dr	James	Mittra	University of Edinburgh
Mr	Jonathan	Mogford	Medicines and Healthcare products Regulatory Agency
Dr	Natalie	Mount	Cell Therapy Catapult
Dr	Gopalan	Narayanan	Medicines and Healthcare products Regulatory Agency
Dr	Maria	Pascual	Tigenix
Dr	Jonathan	Pearce	Medical Research Council
Dr	Bina	Rawal	Association of the British Pharmaceutical Industry
Mr	Ian	Rees	Medicines and Healthcare products Regulatory Agency
Dr	Ros	Rouse	Economic and Social Research Council
Dr	Jill	Shepherd	Human Tissue Authority
Dr	Sue	Simpson	University of Birmingham
Mr	John	Sinden	Renuron
Ms	Imogen	Swann	Human Tissue Authority
Prof	Marc	Turner	University of Edinburgh
Dr	Ludovic	Vallier	University of Cambridge
Prof	Fiona	Watt	King's College London
Prof	Andrew	Webster	University of York

Prof	Paul	Whiting	Pfizer
Prof	Martin	Wilkins	Imperial College London
Prof	David	Williams	Loughborough University
Mr	Dylan	Williams	Academy of Medical Sciences
Ms	Alison	Wilson	Cell Data Services
Prof Sir	Kent	Woods	Medicines and Healthcare products Regulatory Agency
Dr	Naho	Yamazaki	Academy of Medical Sciences

[1] Delegates listed are those who accepted to attend