の無菌操作を行う場所である。また，清浄度管理区域とは，製品等の調製作業を行う場所，及び滅菌される前の容器等が作業所内の空気に触れる場所である。

以下は，薬局等構造設備規則の第4節 再生医療等製品の製造業の第14条に示された項目である。

薬局等構造設備規則

第4節　再生医療等製品の製造業

第14条　再生医療等製品製造業者等の製造所の構造設備（抜粋）

第1号：製品を製造するのに必要な設備及び器具を備えている

第2号：作業を行うのに支障のないよう配置，清掃及び保守が容易なもの

第5号：原料の受入れ，製品の保管等を行う区域の必要な構造及び設備を有する

第6号：作業所の規定に適合

第7号：作業室の規定に適合

第8号：温度及び湿度を維持管理できる構造及び設備を有する

第9号：清浄度管理区域，無菌操作等区域の規定に適合

第10号：動物又は微生物を用いる試験を行う区域，製品の製造に必要のない動物組織又は微生物を取り扱う区域は，区別され，空気処理システムが別系統

第11号：無菌操作を行う区域におけるフイルターにより処理された清浄な空気を供し，かつ，適切な差圧管理を行うために必要な構造及び設備を有する

第12号：病原性を持つ微生物等を取り扱う区域における適切な陰圧管理を行うために必要な構造及び設備を有する

第13号：器具の洗浄，消毒及び滅菌のための設備並びに廃液等の処理のための設備を有する

第14号：空気処理システムとして，微生物等による製品等の汚染を防止するために適切な構造のもの

第16号：使用動物を管理する施設の規定に適合

第17号：製品等及び資材を衛生的かつ安全に貯蔵するために必要な設備を有する

第18号：貯蔵設備は，恒温装置，温度計その他必要な計器を備えたもの

第19号：試験検査の設備及び器具を備えている

再生医療等製品の製造管理及び品質管理の基準（GCTP省令）が新設されることで，新しい分野の再生医療等製品の管理に関する省令が整備された。この省令はGMP省令をベースとして，再生医療等製品に特化した事項が上乗せとして盛り込まれている。下記にGCTP省令の条文を一覧として載せたが，「品質リスクマネジメント」，「ベリフィケーション」，および「製品の品質の照査」の項目が，省令としては初めて記載された。

GCTP省令（再生医療等製品の製造管理及び品質管理の基準に関する省令）

（平成26年厚生労働省令第93号）

第1条　趣旨
第2条　定義
第3条　適用の範囲
第4条　品質リスクマネジメント
第5条　製造部門及び品質部門
第6条　製造管理者
第7条　職員
第8条　製品標準書
第9条　手順書
第10条　構造設備
第11条　製造管理
第12条　品質管理
第13条　製造所からの出荷の管理
第14条　バリデーション又はベリフィケーション
第15条　製品の品質の照査
第16条　変更の管理
第17条　逸脱の管理
第18条　品質等に関する情報及び品質不良等の処理
第19条　回収処理
第20条　自己点検
第21条　教育訓練
第22条　文書及び記録の管理
第23条　記録の保管の特例

下線：GCTPで新たに規定された項目
波線：再生医療等製品の特性を踏まえた事項が考慮された項目

(1)「品質リスクマネジメント」について

GMP省令では課長通知として示されていたが，GCTPでは省令に明記された（第4条）。再生医療では，生きた細胞など，多様で複雑な品質特性を示す生体材料を扱うため，品質リスクを科学的に評価し，品質リスクマネジ

メントを活用することで，より高度な品質保証を達成しなければならない。製品の開発初期から製造販売が終了するまでの全期間にわたり，製品の品質に対するリスクについて，適切な手続きに従い評価・管理を行うことが求められる。製品の製造手順及び製品品質の継続的改善を促進する主体的な取り組み（第2条関係解説[3]）であり，リスクアセスメント，情報共有，レビュー等を体系的に運用していくことで，問題の発生を未然に防ぐことが期待される。

品質リスクマネジメントは，変更管理におけるバリデーションの設定，原料等の委託先の選定及び管理手法，環境モニタリングのサンプリングポイントの設定やプロセスシミュレーションテスト設定等，多岐にわたって活用されるべきであるが，品質に対する潜在リスクの特定や製造プロセスに対する科学的な評価及び管理を自らの責任で確立することに留意しなければならない。

品質リスクマネジメントの基本的考え方
（GCTP省令第2条及び第4条）

「品質リスクマネジメント」とは，製品の初期開発から製造販売が終了するまでの全期間にわたり製品の品質に対するリスクについて適切な手続きに従い評価，管理等を行い，製品の製造手順等及び品質の継続的改善を促進する主体的な取り組みをいうものであること（第2条関係解説[3]）。

(1) 製造業者等が，製造管理及び品質管理を行うに当たって，品質リスクマネジメントの活用を考慮することを規定したものであること。品質リスクマネジメントは，製品の適正な製造管理及び品質管理を構成する要素として品質に対するリスクの特定，分析，評価，低減等において主体的に活用するものであること（第4条関係解説(1)[3]）。

(2) 品質システムにおいて，製造手順等に係る各工程すべてを見渡した上で，そのうちリスクマネジメントの対象とすべきもの及びその結果を適用すべきものについて検討すべきものであること（第4条関係解説(2)[3]）。

(2)「ベリフィケーション」について

再生医療等製品の早期承認制度を踏まえて，やむを得ない理由によりバリデーションを行うことができない場合には，「ベリフィケーション」を行うことと記載（GCTP省令第14条）している。

再生医療等製品の製造工程の開発では以下のように，既存のプロセスバリデーションの枠組みは適用できない場合も考えられる。1）ヒト由来の組織，細胞が原料となる場合，製造経験が限られるため，その場合の開発アプローチが確立していない。2）製造工程の変動を制御するためには，どのような観点で開発を進めれば良いかのノウハウが乏しい。3）製造工程の稼働性能についての評価の考え方が確立していない。4）恒常的に目的とする品質を製造するための評価の考え方が確立していない。

このように，変動要因の特定が困難で科学的な管理規格の妥当性が十分に説明できないため，恒常的に目的とする品質を製造できていることを3ロットのプロセスバリデーション[注1]データで評価することができない場合には，ベリフィケーションを実施して，目的とする品質に適合した製品を製造するための管理方法が確立してから，バリデーション報告書を作成する必要がある。（「再生医療等製品の製造管理及び品質管理の基準等に関する質疑応答集（Q&A）について（その2）」平成27年7月28日薬食監麻発0728第4号[6]）

注1）プロセスバリデーション：工業化研究の結果や類似製品の製造実績等に基づき，あらかじめ特定した製品の品質に影響を及ぼす変動要因（原料及び資材の物性，操作条件等）を考慮した上で設定した許容条件の下で稼動する工程が，目的とする品質に適合する製品を恒常的に製造するために妥当であることを確認し，文書化すること。検証の方法は，原則，実生産規模での製造スケールとして，3ロット又は製造番号の繰り返し又はそれと同等以上の手法とする。

再生医療等製品を製造するにあたって，ベリフィケーションを採用するためには，製品の品質に係る変動要因は十分に特定されていないものの，製造工程の設計に関する理解を深める必要があるとともに，管理戦略に基づく製造管理及び品質管理の方法が適切に製造販売承認書に規定されることが前提である。また，製品の製造前までには，製造設備機器の適格性評価（DQ，IQ，OQ及びPQ），当該施設における試験法に関する分析法バリデーション及び製造設備機器の洗浄バリデーションが検証されている必要がある。その上で1）ベリフィケーションマスタープラン（ベリフィケーションを確実に実施して，ベ

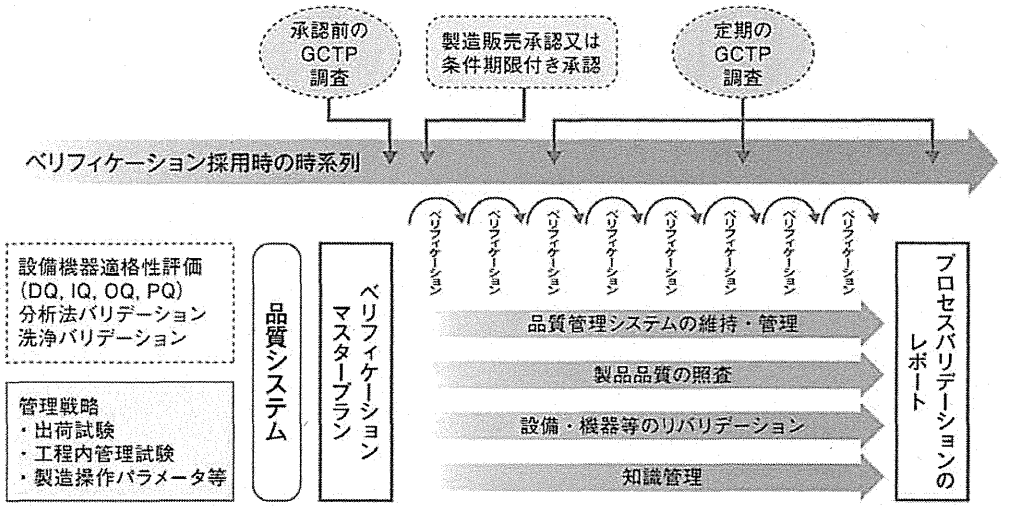

図4　再生医療等製品のベリフィケーションの概念図

リフィケーションの結果を定期的かつ総合的に評価し，目的の品質の製品が一貫して製造できていることを確認しつつ，最終的に恒常性を担保できる製造管理・品質管理の方法などの管理戦略を確定することを目的とする）を作成し，2）定期的な製品品質の照査を実施し，3）変更や逸脱を適切に管理できる知識管理を実行する。また，ベリフィケーションマスタープランには，1）出荷試験，工程内管理試験，製造の操作パラメータ等の評価及び確認をするための管理戦略が含まれており，2）定期的な製品品質の照査に係る具体的な評価頻度，評価項目，評価方法が計画されていること，3）プロセスバリデーションとしての最終的な検証方法について記載されていることなどが必要である[4]。

(3)「製品の品質の照査」について

製品の品質の継続的な改善を図るために，製造工程の一貫性及び製品等の規格の妥当性について検証することを目的として，定期的又は随時，「製品の品質の照査」を行うこととして新たにGCTP省令第15条に記載された。「照査」とは，製品の品質に対して，あらかじめ定めた手順に基づき設定された目標を達成する上での妥当性及び有効性を判定し，これを文書化するとともに継続的改善を促進する取り組みをいうものである（第2条関係(9)[3]：照査の定義）。「製品の品質の照査」は，定期的又は随時，製品の品質に関する結果，状況等について監視測定及び分析を行うことにより，製品が適切に管理された状態で製造されているか，又は改善の余地があるかを確認するために実施するものである（第15条関係(2)[5]：実施の目的とその手法）とされている。

このように，再生医療等製品のような製造管理・品質管理の方法が一般的な医薬品に比較し難しいと考えられる製品は，品質システムを実効的にするために，品質リスクマネジメントの多岐にわたる活用と製品の品質の照査による継続的な改善の取り組みは不可欠である。さらに，これらを運用するためには，細胞培養をはじめとする高度な技術と品質管理を維持する知識管理も重要な意味を持つ。例えば，再生医療における製造では機械化が進んだ医薬品製造工程と比較して，作業者個人の技量が品質に大きく影響する場合があり，正確な細胞培養作業，細胞の状態把握，適格な分析機器操作及び判定などに加えて，作業手順書や技術移管計画書・報告書の作成等も，目的とする品質達成に重要となる。開発段階から上市まで，これらに関する再生医療等製品に特有の技術要件について品質リスクマネジメントを活用しながら得られた知識や情報を，的確に共有し利用できる知識管理は鍵を握っているといえる。加えて，上市後に製品を製造し続けている期間においても，これらの知識を利用し品質リスクマネジメントを活用した変更管理の評価や逸脱の改善措置，製品の品質の照査及びバリデーションやベリフィケーションの結果などから，さらに得られる情報を解析した知識を蓄積していくことは，製品のライフサイクル

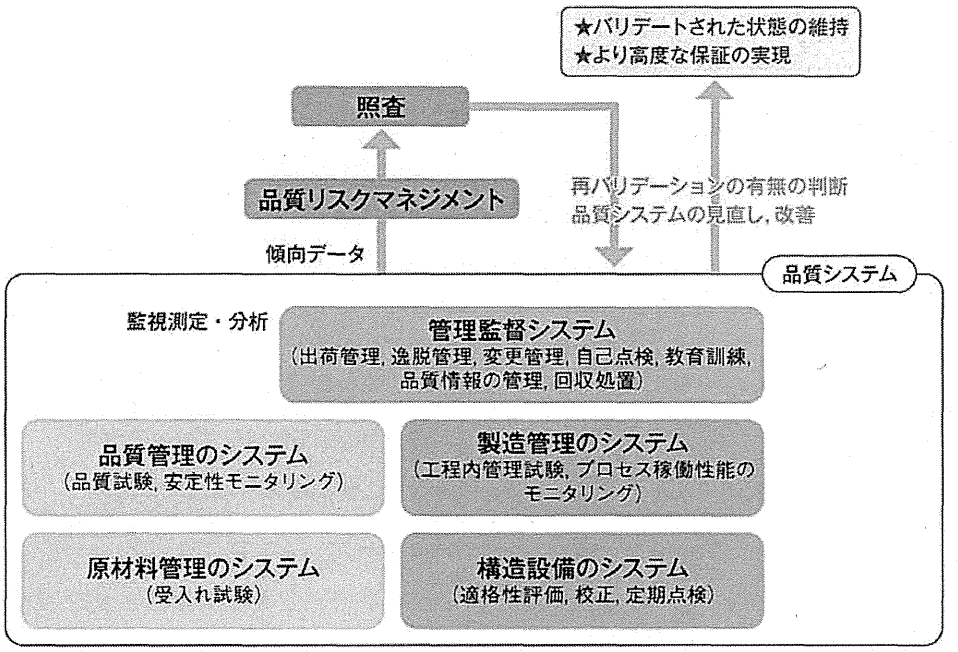

図5　製品の品質照査

を通じて品質を維持するために非常に重要である。以上の考え方はPMDA科学委員会CPC（Cell Processing Center）専門部会で「再生医療等製品の品質確保における基本の考え方に関する提言」として取りまとめられているので参照いただきたい[6]。

3 「再生医療等安全性確保法」に基づく調査について

上述のように再生医療等安全性確保法では，特定細胞加工物の製造施設は，「許可」（国内）または「認定」（海外）を取得することが求められる。構造設備の基準は「医薬品医療機器法」と同様に，無菌操作等区域と清浄度管理区域が区別されており，特定細胞加工物の製造を行うために必要な構造設備基準を掲げている。

PMDAにおける調査は，構造設備の基準に沿った設備・機器の設置状況の確認のいわゆるハード面のみを視点とした調査である。留意いただきたいのは，構造設備を構築する際は，製造における動線を考慮した上で設計する必要があるなど，ハードの適切性はソフトの運用管理とともに成立するものである。

本来，製造施設が構造設備を構築する際や設備を適切に維持管理していくためには，あらかじめ製品の特性に応じた製造プロセスと手順とその動線，製造施設の組織体制や文書等のソフト面の管理も構築されていることが重要となる。したがって許可の適否の判断事項ではないが，製造活動を行うにあたっては，以下に列記した最低限の事項については検討しておくことが重要と考える。

(1) 組織が明確になっているか？
  1. 各部門の役割，職員の役割の明確化と文書化
  2. 各責任者の責務の明確化と文書化及び指名
(2) 製造や試験，衛生管理に関する文書が作成されているか？
  1. 文書体系に関する規定
  2. 作業を変更した際，その変更内容，理由，いつから変更したことがわかるようになっているか？
  3. 逸脱が発生した場合の状況や，その原因調査を実施したことを記録することにしているか？
  4. 上記の文書や記録が必要な年限保管されることになっているか？
(3) 複数の検体，特定細胞加工物を扱う場合の取り違い防止策が設定されているか？
(4) 複数の特定細胞加工物を同一の設備，機器，器具を用いる場合に交叉汚染を防止するための方策が設定されているか？
(5) 工程や環境等からの雑菌汚染に対する防止策が取られているか？

(6) 医療機関との取り決めがあり，輸送条件等，品質確保に必要な条件が設定されているか？ またその記録を残すようにしているか？

(「再生医療等の安全性確保法における細胞培養加工施設の構造設備基準チェックリスト」[8]より)。

4 特定細胞加工施設の調査申請と調査の現状

平成26年11月「再生医療等安全性確保法」施行後の許可・認定状況について，本年7月現在の申請受付総数は43件である。このうちで調査を終了して報告内容が整理されたものは21件である。これらを申請された施設を大きく分類すると，(1) 国公立研究開発法人，独立行政法人および公益財団法人である公的医療施設，(2) 国公立・私立大学医学部の付属病院関連施設，(3) 個人病院，クリニック付属施設，および (4) 株式会社，民間企業等の施設となる。申請の内訳は，(1) の公的機関は10件(23%)，(2) の医学部大学関連施設は13件(30%)，個人病院関連施設は3件(7%)，および企業関連施設は18件(41%)であった。

これまでの調査において以下のような構造設備に対する不備事例があった。

1) 調査時に製造に必要な設備が未設置であった(例：製造に必要な顕微鏡が設置されていない。温度管理が必要な倉庫に温度測定機器が設置されていない)。
2) 製品の評価試験が外部委託であり，委託先の試験エリア図面や試験機器の情報が確認できなかった。

また，ソフト面の運用により，ハード面の改善を要求するには至らないと考えられる場合については，運用管理を適宜見直した後に，ハードの改善の要否について判断するよう推奨している。例えば，保管エリアに，さまざまな物品を保管しているために，製造に必要な資材や製品との混同の恐れや，合格・不合格などのステータス管理をして保管するには手狭の状況が見受けられる。整理整頓をすることで十分な面積を確保するハードの改善の要否を判断するよう推奨している。

本来，原料・資材の保管スペースも製造数の見込みに併せて設計しておくことに留意すべきである。また，細胞組織や製品と，廃棄物や製造に使用しない動物の搬入の動線が交叉する設計の場合，搬入の方法やタイミングにより交叉汚染防止が確保できるかなどを検討し対策を講じた上で手順化しておく必要がある。

5 厚生労働科学研究での取り組み

法改正により開始した再生医療等製品や特定細胞加工物の制度に対しては，まったく新たな分野の対応であり，それらの特性を踏まえた製造管理・品質管理のあり方やGCTPの理解については，検討すべき課題が多い。今後，ますます再生医療を安全に迅速に普及していくために，この課題を研究するための厚生労働科学研究に取り組んでいる。再生医療等製品に関しては，H26年度から「GMP/QMS/GTP及び医薬品添加剤のガイドラインの国際整合化に関する研究」(研究代表者：独立行政法人医薬品医療機器総合機構　櫻井信豪)の中で，ガイドラインの改訂や医薬品，医療機器及び再生医療等製品の製造管理・品質管理の質の向上のための研究を行っている。この研究班の成果として，GCTP省令に係るQ&Aを発出している[7,9]。また，再生医療等製品の他，特定細胞加工物も含めた研究としては，平成26年度から「特定細胞加工物／再生医療等製品の品質確保に関する研究」が進められている。この研究班の代表は，国立医薬品食品衛生研究所医療機器部部長の新見伸吾氏，研究分担者として大阪大学生物化学工学教授の紀ノ岡正博氏が「無菌性保証及び工程等の微生物等汚染リスク低減のあり方に関する研究」を，また国立医薬品食品衛生研究所再生・細胞医療製品部部長の佐藤陽治氏が「製造・流通上の変動要因等を考慮した製品・原料資材の規格及び試験検査のあり方に関する研究」をテーマとし，研究協力者には一般社団法人再生医療イノベーションフォーラムをはじめとする業界団体，厚生労働省医政局研究開発振興課と医薬食品局監視指導・麻薬対策課，PMDA等が参加している。研究成果として品質保証の考え方，基本的な方針等を示すことにより，製造業者等の理解に寄与することが期待される。

まとめ

冒頭で述べたように，「医薬品医療機器法」によって再生医療等製品の安全性が担保されることを前提に有効性の推定される段階で承認する早期制度が構築され，一方で再生医療としては「再生医療等安全性確保法」のもとで，自由診療や臨床研究においても安全性の確保を義務づける基準が新たに設けられたことで，迅速性と安全性の両面から再生医療を促進する環境が整ってきている。しかしながら，再生医療等製品の特性を考慮した製造管理・品質管理のあり方や品質確保については，使用する細胞自体が未知な部分が多いことからまだまだ課題が多い。製造管理（無菌保証，交叉汚染防止，取り違い防止）や品質管理手法の確立，品質リスクマネジメント，バリデーション／ベリフィケーション，製品品質の照査を実施していくことで品質の恒常性を目指すことはもちろんのこと，未知なる細胞自体の品質確保を可能とするためには，製品のライフサイクル全体において得られる知識をしっかり管理していくことが重要な要素である。

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Building on our own potential: a UK pathway for regenerative medicine

A report from the Regenerative Medicine Expert Group

Contents

1. Foreword

In its report on regenerative medicine, the House of Lords Science and Technology Committee described "advanced therapies" as "*methods to replace or regenerate human cells, tissues or organs in order to restore or establish normal function. This includes cell therapies, tissue engineering, gene therapy and biomedical engineering techniques, as well as more traditional treatments involving pharmaceuticals, biologics and devices.*" Since living cell-based therapies have their own unique challenges with respect to translation and commercialisation, this report principally focuses on cell therapies, and in particular their role in regenerative medicine.

Regenerative medicine involves the use of some of the most advanced therapeutic technologies of the 21st century. The rapid pace of the supporting science is likely to see its application across ever increasing fields of clinical practice. The UK has already made a substantial investment in regenerative medicine through support by the Research Councils, by the National Institute for Health Research and particularly the NIHR, Biomedical Research Centres (BRCs) and Units (BRUs).

As with many other emerging technologies in the life sciences sector the UK has the opportunity to be the global leader in this area with an academic, clinical and industrial infrastructure to make it happen. Moreover, the NHS is an obvious partner in cultivating an environment that supports early development, adoption and spread of these new technologies.

Our report has the primary purpose of providing advice on what more needs to be done to bring this about. This will involve ensuring proportionate and streamlined regulation; an approach to product development that maximises the expertise in the academic, commercial and healthcare delivery sectors reflecting the shared objectives of all stakeholders; and a model for delivery to patients that builds upon the excellent work that is already taking place in the UK. The members of the Expert Group hope its report describes a direction of travel that will place the UK at the forefront in the application of this exciting science.

I would like to thank the members of both the Group itself, and of the three sub-groups, for all their many contributions. I would especially wish to express my appreciation to the chairs of the sub-groups including Mr Keith Thompson (Regulation and Licensing sub-group), Dr Nick Crabb and Ahmed Syed (Evaluation and Commissioning sub-group) and Professor Chris Mason (Delivery sub-group) for all their work. Finally I wish to place on record the Expert Group's thanks to the officials in the Department of Health, and in other government departments, for their excellent support as well as their timely and expert contributions.

Sir Michael Rawlins
Chair, Regenerative Medicine Expert Group

December 2014

2. Introduction

In July 2013, the House of Lords Science and Technology Committee published a report of their inquiry into regenerative medicine. This called for a regenerative medicine expert working group to be established to develop an NHS regenerative medicine delivery readiness strategy and action plan, and report back to the Secretary of State for Health by December 2014. In their joint response to the report, on behalf of the Government, the Department of Health and Department for Business, Innovation and Skills agreed to this recommendation and the Regenerative Medicine Expert Group (the Expert Group) was convened, with a membership from across the UK, including representatives from each of the four countries. The Regenerative Medicine Expert Group was given the remit to monitor progress on the Government's response to the House of Lords inquiry; and to develop, in partnership with other stakeholders, a strategy for regenerative medicine in the NHS and provide an action plan.

This report is the culmination of the work carried out by the Expert Group. It provides an update on the progress that is being made to support the growth of regenerative medicine in the UK, for the benefit of NHS patients and the economy, and advice on what more needs to be done. The report, as is set out, follows the development pathway of a product from clinical trials, to commissioning through to routine use in the NHS.

The term 'regenerative medicine' refers to methods that replace or regenerate human cells, tissues or organs in order to restore or establish normal function. The term includes cell-based therapies, tissue engineering and gene therapy. In reality, the term can also be applied to established therapies, such as haematopoietic stem cell transplantation to treat life-threatening blood disorders, through to emerging new technologies that, for example, use cells to repair or replace damaged or lost tissue.

There is rapid progress being made across a wide spectrum of cell-based therapies, and whilst the report principally focuses on their use in regenerative medicine, the opportunity to realise the potential of cell therapy across the whole breadth of medicine should be seized.

Regenerative medicine is going to be important in future medicine – delivering step changes in the way we treat disease and making a significant economic contribution.

Economic benefit is an area where regenerative medicine could deliver. If we get the environment right, an emerging innovation ecosystem could support the growth of a healthy and robust regenerative medicine industry in the UK. Investment is happening. The UK Cell Therapy Manufacturing Centre, which will be based at Stevenage Bioscience Catalyst – an open innovation campus – will manufacture late phase clinical trial and commercial supply of advanced therapeutic medicinal products including cell and gene therapies. It will also incentivise the private sector to invest in UK-based firms and is anticipated to generate £1.2 billion of private sector revenue by 2020.

Benefits to the UK economy, however, will need to be won in an international market. That is why we need to be able to compete, and be open to partnership, at a national, European and international level. Latest figures from UK Trade and Investment show that, in 2012, annual revenue from regenerative medicine products surpassed the $1 billion mark. The global regenerative medicine market is predicted to grow significantly.

The report takes a UK-wide view, unless otherwise specified, but accepts that different approaches may be needed for the adoption of regenerative medicine in healthcare that reflect the delivery systems in each country of the UK.

The Expert Group's evidence gathering and analysis were mainly delivered by three sub-groups dealing with: a) regulation and licensing; b) evaluation and commissioning; and c) delivery. The members and Terms of Reference of the Expert Group and members of each of its sub-groups are in the annexes to the report.

3. Executive Summary

As is the case in most life sciences, the UK is well placed to consolidate and build upon its position as a world leader in regenerative medicine. We have the industrial base, the academic excellence and the clinical know-how that is necessary. We also know what success looks like, from the advances in the treatment of leukaemia, to building new tracheas and restoring eyesight after corneal damage. These great success stories show what can be achieved through the collaborative efforts of impassioned individuals. Much of this work is underpinned by the NHS. Its unique position as a single national healthcare provider, our ability to access patient data and an established logistics system are benefits that should not be undervalued.

Cell therapy developers from the academic community, and from industry, indicated to the Expert Group that the current system of multiple, and sometimes overlapping, regulatory advice should be streamlined. We therefore welcome the announcement by the four regulators in the field (the Health Research Authority (HRA), the Human Tissue Authority (HTA), the Human Fertilisation and Embryology Authority (HFEA) and the Medicines and Healthcare products Regulatory Agency (MHRA)) that the MHRA's Innovation Office will be the portal for a 'one-stop shop' service to provide a single point of access for all regulatory queries concerning regenerative medicines.

However, regenerative medicine operates in a global environment. Many countries, especially the United States and Japan, are keen players in the field and we need to ensure that we compete as well as collaborate. Within the European Union the European Medicines Agency (EMA) in most cases provides a single portal to the European market. Here, the international standing of the MHRA helps the UK retain its influence and also provides an avenue for international companies to gain a foothold in European markets, preferably with the UK as their European home. That is why the report calls for the MHRA to press for an EU-wide consensus on the following points:

- The removal of any disparity in categorisation across the Member States for products which straddle the boundary between cellular therapies regulated under the EU Tissues and Cells Directive and those regulated as medicines under the Advanced Therapy Medicinal Products (ATMP) Regulations (somatic cell therapies, tissue engineered products, gene therapy products and combination products). This should include consideration of a European classification scheme coordinated by the EMA's Committee for Advanced Therapies (CAT) and subsequently adopted by all Member States.
- Changing the definition for the application of the Hospital Exemption Scheme from 'non-routine' to 'meeting an unmet clinical need where no authorised products are available'; and that use of an unlicensed product should be disallowed if there is a licensed product available and it meets the clinical needs of patients.
- Broadening the scope of the quality and non-clinical data certification scheme, when the ATMP Regulations are reviewed, to all types of applicants.
- A review of the cost structure both for scientific advice and to assist with the affordability of ongoing regulatory fees.
- 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.

More needs to be done on standardisation of approach and reducing the regulatory burden wherever possible. This is especially important for clinical trials where further efforts are needed to make approvals, funding and recruitment more effective. The Expert Group proposes that regulators build on current initiatives and give further consideration to the following:

- Advice about the classification and associated requirements for trials involving gene modification should be made available to researchers through participation of the Department for Environment, Food and Rural Affairs (Defra) and the Health and Safety Executive (HSE) in the regulatory 'one-stop shop' for regenerative medicine.
- An evaluation of the 'one-stop shop' service after its first year that is informed by the experiences of its users, and the findings used to make necessary improvements.
- The possibility of incorporating applications needed for clinical research involving gene therapy products, genetically modified micro-organisms and genetically modified organisms (GMOs) into the HRA's existing Integrated Research Application System (IRAS) should be explored.
- Defra should examine best practice in applying GMO legislation in other EU countries to ensure that UK requirements are comparable and proportionate.

The report is clear throughout that every effort should be made to build on what is already in place. However, further steps are needed to ensure that standardisation of processes, and streamlined regulation, are guiding principles in advancing regenerative medicine. This is why the Expert Group advises that, given there is already a network of appropriately regulated centres with Tissues and Cells licences or Blood Establishment Authorisations, the UK should press for a consistent approach, throughout the EU, to allow the use of centres with either Tissues and Cells licences or Blood Establishment Authorisations for the procurement and mandatory testing of blood components as starting materials for ATMP development.

There are difficulties for researchers in relation to the issue of 'excess treatment costs' which can be a barrier to carrying out clinical trials. The Expert Group strongly recommends that the funding for excess treatment costs for cell therapy trials, is reviewed by NHS England and the NIHR as well as by their equivalents in the other UK regions; and that a mechanism is found to ensure that meeting of these costs is not a barrier to clinical trials or the early adoption of technologies.

In order for NHS patients to benefit from regenerative medicines, robust and effective product evaluation has to be made to inform commissioning decisions. National Institute for Health and Care Excellence (NICE) guidance is essential in speeding up the adoption and spread of high value regenerative medicines in healthcare. However, applying the Institute's appraisal methodology, based on cost utility analysis, to products whose true value may not be known for many years can be challenging, due to the inherent uncertainty of estimating long-term benefit from evidence derived from short-term studies.

The Expert Group was therefore pleased to learn that NICE has agreed to undertake 'mock' technology appraisals on regenerative medicine products. We encourage the Institute to consider the findings from these studies with a view to assessing whether changes to its methods and processes are needed.

Evaluation and commissioning, as with all steps of the product development pathway, need to be supported by clear, up-to-date and accessible advice and guidance. NICE already provides scientific advice in many areas and the Expert Group calls on the Institute to develop advice focused on the needs of small and medium sized regenerative medicine companies and explore options for supporting their access to NICE scientific advice.

Initiatives such as this are important if we are to get innovative new therapies to patients in the fastest possible time. Early product evaluation

alone, however, is insufficient to speed up this process. Often, the risks of introducing a new, probably disruptive, therapy can be seen as too great for either the company (especially small and medium sized enterprises (SMEs)), or for the relevant healthcare commissioner. Addressing this issue is extremely important if we truly wish to see the NHS as a natural partner in innovation adoption and spread. The report therefore calls upon government to engage with key stakeholders with a view to developing an innovative business model that supports the early adoption of regenerative medicines. The Expert Group recognises that this will be difficult, in a time of budgetary constraints, and understands that imaginative solutions will be required.

To support these efforts, it will be necessary for commissioners and clinicians to have access to quality information, knowledge and advice. All four countries of the UK need to take account of this when developing services to deliver regenerative medicine. For example, NHS England has established a working group on regenerative medicine and the Expert Group calls for this to evolve into a formal 'Clinical Reference Group (CRG) for regenerative medicine' as new products are identified for consideration by NHS England. The CRG should include clinicians covering a wide range of specialties and experience in regenerative medicine (e.g. oncologists, cardiologists, ophthalmologists, orthopaedic surgeons and haematologists) in order to provide specific expertise, insight and advice on regenerative medicine products. Other UK countries should make comparable arrangements for their own healthcare systems.

The final, and arguably the most important, part of the journey, is embedding regenerative medicine in the NHS. In the initial phase, the use of regenerative medicines will be carried out in a few recognised Centres of Excellence located in leading hospitals. These are likely to have established relationships with Academic Health Science Networks and NIHR Biomedical Research Centres and Units. Coordination and collaboration in the use of regenerative medicines should be led by the centres themselves, who should be champions as well as practitioners.

The Expert Group believes that the establishment of Centres of Excellence is essential if we are to build a concentrated, critical mass of knowledge, skills and therapeutic know-how that will be the foundations on which regenerative medicine can be established. The report recommends that the Department for Business, Innovation and Skills and the Department of Health, together with NHS England, engage with relevant partners to further develop the concept of Cell Therapy Centres of Excellence, and determine how they should be identified and the options for a collaborative development framework. This should include their role in improving the UK cell therapy clinical trials infrastructure as well as the delivery of treatments to NHS patients.

As already mentioned, the whole system delivery model of the NHS brings great benefits. The relevant UK blood service authorities already have cell processing, storage and delivery facilities and expertise alongside other, more local, delivery systems. A logistics system will need to be designed to respond to the specific requirements of regenerative medicine, from harvesting and processing of cells through to near application preparation.

Building on existing networks to address the needs of regenerative medicine should provide access to systems already in place and that are likely to be compliant with all necessary quality standards. The report therefore calls for the UK blood and tissue services in partnership with the Cell Therapy Catapult and other stakeholders, including industry, to undertake analyses of existing infrastructure to assess the options for the delivery of a cell therapy procurement, manipulation, storage and distribution network that supports the development of Centres of Excellence in cell therapy and its application. This should build on existing arrangements including, where possible, the global infrastructure provided by specialist carriers and be informed by the outputs from the Cell Therapy Catapult's Seamless Freight Initiative (a programme designed to aid the tracking and control of

cell therapies on their journey from a donor, through manufacturing and distribution, to an individual patient).

The success or failure of adoption of regenerative medicine in the NHS is also likely to be dependent on the level of education and training of its staff. Work will need to be done, particularly by the Royal Colleges, Health Education England and the healthcare systems across the UK, to ensure that appropriate training is available. To be effective, any education and training will need to encompass raising general awareness when introducing new technologies into healthcare, through in-depth requirements tailored to the needs of individual disciplines. Likewise, in developing the supply pipeline, the need to train scientific staff in translational research and manufacturing will be required. Once again, the UK is in an enviable position, as there is a reservoir of highly trained scientists already in place that could fill this need. The Research Councils and NIHR will also need to play a leading role in this matter.

The collection of validated, standardised robust data on the application of regenerative medicine, the patients who receive it and the products used will be essential in quality assurance and the long-term assessment of efficacy and safety. The report calls for consideration to be given to a central registry of patients treated with cell therapies; and for clinicians to provide follow-up information to capture healthcare outcomes. Furthermore, the Expert Group recommends that the format and use of the Cell Therapy History File, recommended in the HTA/MHRA report on joint working, and which has been further developed as a template by the Cell Therapy Catapult, should be implemented across the UK and promoted for EU-wide adoption.

Finally, to reflect the importance of regenerative medicines for future healthcare and economic growth, the Expert Group strongly recommends the establishment of a Ministerial Group, similar to the Ministerial Medical Technology Strategy Group and Ministerial Industry Strategy Group, for regenerative medicine.

4. Development

4.1 Introduction

The regulation of regenerative medicines is a vital part of their development. Properly and proportionately carried out, it provides assurances about quality, efficacy and safety as well as giving public confidence that appropriate procedures have been followed. In addition, it offers an endorsement for industry which is a *sine qua non* for opening up access to the market.

Where the cells have only been minimally manipulated and used for homologous treatment they fall under regulation by the EU Tissues and Cells Directive (EUTCD) and are regulated in the UK by the Human Tissue Authority (HTA). Such products are not classified as Advanced Therapy Medicinal Products (ATMPs) and are not regulated as medicines. Consequently, there is no legislative requirement for clinical trials, marketing authorisation, or manufacture in accordance with Good Manufacturing Practice (GMP) for these therapies. Under EUTCD, however, a controlled processing environment (air quality equivalent to GMP) is required, as is a mechanism for evaluating the quality and safety of these cell-based products. Within the UK, this is assessed via authorisation of a Preparation Process Dossier by the HTA.

Cell-based therapies that involve substantial manipulation and/or are used for non-homologous applications are classified as ATMPs. In the UK, the regulation of ATMPs is not the duty of a single body. Procurement and testing of starting materials may be regulated by the Medicines and Healthcare products Regulatory Agency (MHRA) under the EU Blood Directive (EUBD), the HTA (for non-gamete derived tissues and cells), or the Human Fertilisation and Embryology Authority (HFEA) (for human embryonic stem cells). Ethical approval for clinical research is the responsibility of the Health Research Authority (HRA). Approval for clinical trials of medicines and devices in the UK is the responsibility of the MHRA; and the granting of marketing authorisation is made by the European Commission following a favourable opinion of the Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP). For this category of medicinal product, in addition to the standard provisions for medicines legislation, there are specific EU ATMP Regulations.

Furthermore, at various points in the process, other agencies may have regulatory oversight, such as Defra (for genetically modified products) as well as the Health and Safety Executive (HSE) on release of products into the environment. Ensuring that the process is as streamlined and simple as possible, with adequate advice and support for developers seeking to take their products through the various stages of clinical development, is crucial.

4.2 Clinical trials – the approval process, infrastructure and funding

Clinical trials are authorised by the Competent Authorities of Member States. For the UK, the Competent Authority is the MHRA. Timely delivery of properly designed and powered clinical studies, usually over multiple centres, is key to facilitating the development of the cell therapy field whether undertaken by academia and the NHS or by commercial entities.

The HRA was established to streamline the approvals processes for both ethical review and governance arrangements. A feasibility study has demonstrated that an HRA approval, based on a single application, and consisting of an integrated assessment addressing legal and management aspects of research applications plus the Research Ethics Committee (REC) opinion, was feasible.

Therefore, the previous system of multiple applications will be replaced by a new process that will involve one application to the HRA, and an assessment conducted alongside the REC opinion, to provide an HRA approval. This will provide assurance to sponsors, researchers and any NHS organisations hosting research that the necessary legal and ethical aspects of the study have been fulfilled. The implementation of the process will be supported by mechanisms to ensure that this approval is accepted by others (including clarifying that responsibility for audit and inspection findings relating to the approval rests with the HRA rather than local Trusts). This will eliminate duplication of assessment, requirements for extra documentation or further checking. It will provide a basis for unifying the approval system for health research with other regulators and review bodies. The HRA aims to have the new process in place by December 2015.

To gather feedback on the environment for conducting cell therapy trials, a questionnaire was compiled by a working group of the Regulation and Licensing sub-group. It was sent to 42 organisations (15 industry and 27 academic) who have conducted cell therapy trials in the UK since 2011. A total of 19 responses (7 industry and 12 academic groups) were received commenting on a total of 45 cell therapy trials (23 industry and 22 academic) conducted in the UK over this period. Based on the data collected, in addition to the improvements discussed above, other key areas for action were identified. Difficulties had been encountered with costing templates not specifically designed for cell therapies and a lack of expertise on the ground able to handle cells. It was therefore suggested that specific costing templates and contracts be developed for cell therapy trials; and that there should be centralisation of cell therapy trial expertise and processes for efficient and timely trial start-up and recruitment.

Standardised contracts and costing templates are available for clinical trials generally. In order to maximise their value for regenerative medicine, specific guidance should be available on how to use them; and clauses covering requirements specific to cell therapy (such as traceability) incorporated. This would improve the speed and ease of conducting studies in the UK and give researchers the ability to anticipate costs that should be included in grant applications. The NIHR Clinical Research Network (CRN) and the HRA are able to support development and use of these templates which are specific to cell therapy trials.

In order to deliver cell therapy clinical trials, it is recommended to explore ways to access the existing infrastructure to further coordinate and bring together individuals with specialist knowledge across the R&D structure for cell therapy trial delivery. This includes cell therapy suites, clinical trial research nurses and trial coordinators with the aim of reducing the cost and burden to the investigators and improving the speed and delivery of clinical translation for these therapies in the UK.

The question of whole pathway funding of clinical trials is also critical. As the development of cellular therapies progresses, the source of funding moves from the Research Councils and becomes eligible for NIHR support, through frameworks such as the NIHR early translational research infrastructure and the Efficiency and Mechanism Evaluation scheme (EME). Under this arrangement, a grant covers the research costs of conducting the study. However, protocols requiring additional overnight hospital stays for patients as well as additional treatments (such as immune-suppressive therapy) should be identified as either NHS Treatment Costs or NHS Support Costs. NHS Treatment Costs may be either in excess of standard treatment costs or in some cases a saving. The responsible commissioner for the service area (most likely to be Specialised Commissioning) should be involved in research planning before ethical approval has been given to define the costs or savings and the funding model to complete the study. Commissioners have to consider the funding of NHS Treatment Costs in the context of consideration of all competing calls on the commissioning resources. The diminishing availability of financial resources for service development is recognised as a potential real barrier to clinical trial progression. A potential

solution may be to direct specific funding allocated to NHS excess treatment costs for cell therapy trials outside of general commissioning.

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.

Further work still needs to be done to ensure other aspects of the regulatory approval process of studies specifically related to gene therapy products are also streamlined and effective. These include:

- Clarity on whether gene therapy products, specifically gene modified cells and gene therapy viral vectors, are classed as 'genetically modified organisms (GMOs)'; and whether their use in clinical trials constitutes 'Contained Use' or 'Deliberate Release'.
- Defra should ensure that UK regulations are comparable to those of other Member States and do not inadvertently place UK industry and academia at a disadvantage.

The Expert Group therefore 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.**
- **Consolidated guidance on the requirements for cell and gene therapy trials involving GMOs should be produced.**
- **The possibility of incorporating any additional information needed for clinical research involving GMOs into the HRA's existing Integrated Research Application System (IRAS) should be explored.**
- **Defra should examine best practice in applying GMO legislation in other EU countries, so as to ensure that UK requirements are comparable and proportionate.**

4.3 Licensing

Medicines legislation requires that a manufacturer's authorisation, with any necessary Competent Authority oversight, is required for the production of any medicinal product. The requirement for such authorisation brings considerable resource implications for both producers and regulators. Whilst it is acknowledged that such oversight is necessary for medium to high risk manufacturing activities, the Expert Group considered that the requirement to hold a manufacturers' authorisation for low risk, and fully closed, operations could be overly burdensome.

As already described, market access is currently regulated by the EU's ATMP Regulations. This was introduced to provide tailored requirements for a novel class of product, and to allow for their safe and effective development. Within medicines legislation, there is a specific exemption for ATMPs which are prepared on a non-routine basis and used within the same Member State in accordance with a medical prescription for an individual patient ('the hospital exemption'). There is also a more general exemption for medicinal products (including ATMPs) which are used as unlicensed medicines ('specials') and which may only be supplied in order to meet the special needs of an individual patient in response to a *bona fide* unsolicited request from the treating physician.

Whilst the objective of the hospital exemption provision was to develop, and make available, products on a non-routine basis, many in industry are concerned that there is no uniform interpretation of the term 'non-routine'. This potentially allows the product prepared under the Hospital Exemption Scheme to continue to be used when a licensed product has reached the market. This has the potential to undermine the case for commercial investment to develop full marketing authorisation with all the data on quality, safety and efficacy that are normally required.

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.[1]

Measures have recently been introduced to expedite the availability of novel medicinal products. The so-called 'adaptive licensing' (sometimes called 'staggered approval' or 'progressive licensing') pilot project was launched by the EMA in March 2014. Companies, including those developing ATMPs and who are interested in participating in the pilot, should submit ongoing medicine development programmes for consideration. The process will allow the early authorisation of a medicine, in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorisation, to expand access to broader patient populations. The EMA has indicated that they will work with the various health technology appraisal bodies to ensure that licensing and reimbursement are better aligned and should use all opportunities to seek multi-stakeholder input during development and prospectively plan to use the existing flexibilities in the EU regulatory framework.

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.

Within the UK, the Early Access to Medicines Scheme (EAMS) was launched by the MHRA in April 2014. This aims to give patients with life threatening or seriously debilitating conditions access to medicines, including ATMPs, that do not yet have a marketing authorisation and when there is a clear unmet medical need. The scheme is voluntary and the opinion from the MHRA does not replace the normal licensing procedures for medicines.

The quality and non-clinical data certification scheme is another of the measures introduced in the ATMP Regulations. It is designed to provide incentives for small and medium sized enterprises (SMEs) that have been involved in the first stages of the development of ATMPs but may not wish, or lack resources, to conduct clinical trials. Certification that the quality and pre-clinical aspects of the development conform to the relevant regulatory requirements is intended to help SMEs attract funds so as to facilitate the transfer of research activities to organisations with the capacity to further develop and market such medicinal products.

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

The Expert Group believes that there is a need to create a more favourable environment for ATMP developers working in an academic or non-for-profit setting and where the majority of clinical translational work is currently conducted. In addition to an extension to the Certification Scheme detailed above, fee reductions for scientific advice, and fee incentives to reduce the financial impact of post-marketing obligations, should be adopted.

1 MHRA Guidance Note 14 – The supply of unlicensed medicinal products ("specials") 2014