

**Interim UK Regulatory
Route Map for Stem Cell
Research and Manufacture**

Version: 12.03.2009

About this Map

This *Interim UK Regulatory Route Map for Stem Cell Research & Manufacture* is intended to be a reference tool for those who wish to develop a programme of stem cell research and manufacture, ultimately leading to clinical application. The map has been developed by the Department of Health with the support of the Gene Therapy Advisory Committee, Health & Safety Executive, Home Office, Human Fertilisation & Embryology Authority, Human Tissue Authority, Medicines & Healthcare products Regulatory Agency, Medical Research Council, NHS Blood & Transplant Authority, Scottish National Blood Transfusion Service, Advisory Committee on the Safety of Blood, Tissues & Organs, & the UK Stem Cell Bank.

In general, it will not be possible to determine with any degree of certainty the exact regulatory route for a given application without first consulting directly with the appropriate regulatory bodies. To establish the most appropriate regulatory route for a given stem cell therapy, there are a number of key questions to consider first. These are:

Q1. Are the stem cells intended for Human Application? *Discuss with the HTA (enquiries@hta.gov.uk)*

Q2. Will the stem cells be derived from Human Embryo? *Discuss with the HFEA (admin@hfea.gov.uk)*

Q3. Will the cells be Genetically Modified? *Discuss with the HSE (Notificationofficer@hse.gsi.gov.uk)*

Q4. Will the stem cells be manufactured into a Medicinal Product or Investigational Medicinal Product?

Discuss with the MHRA (info@mhra.gsi.gov.uk)

Q5. Is the Product to be Licensed? *Discuss with the MHRA (info@mhra.gsi.gov.uk)*

Q6. Is Animal *in vivo* work required? *Discuss with the MHRA (info@mhra.gsi.gov.uk) & Home Office (020 7035 4785)*

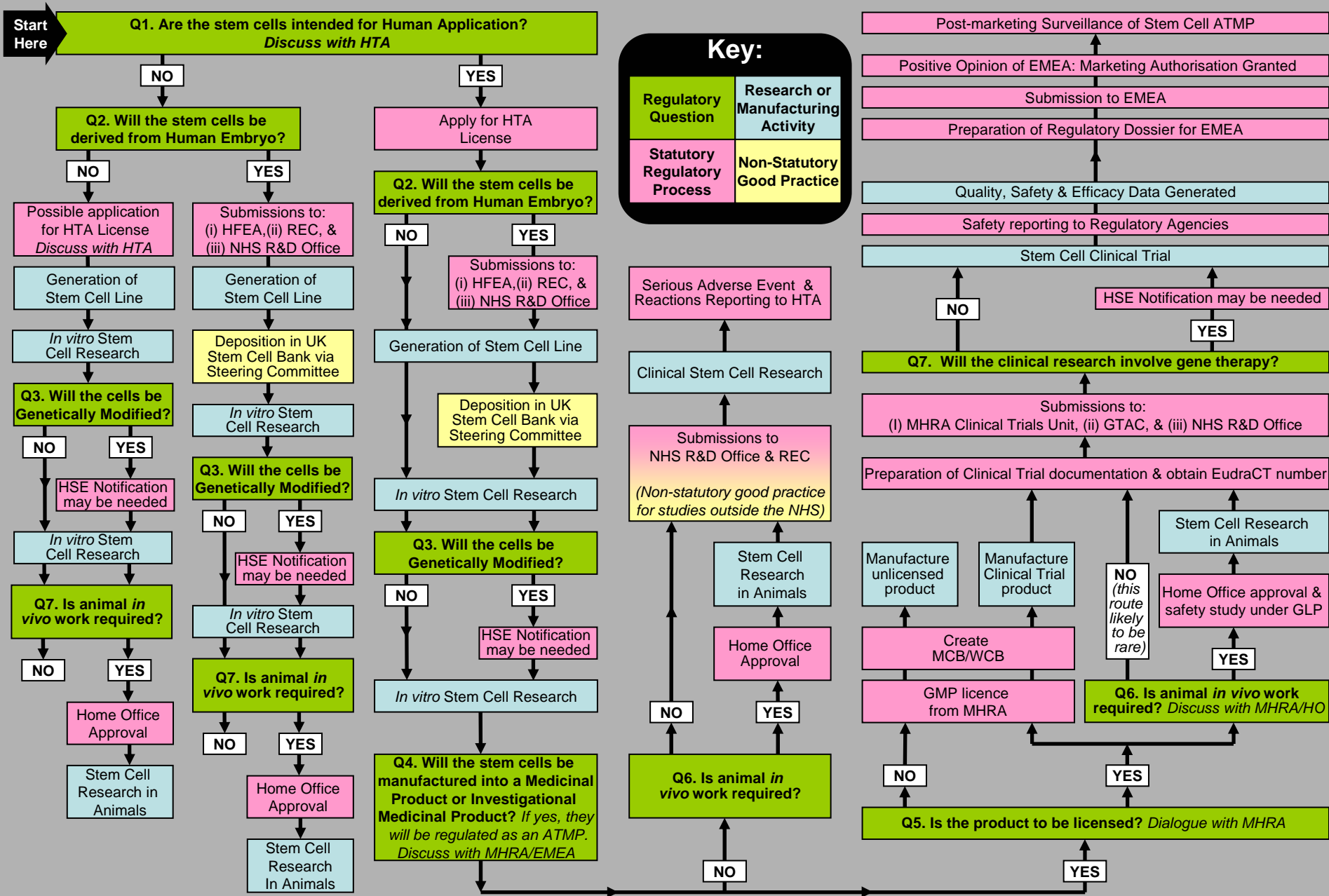
Q7. Will the clinical research involve Gene Therapy? *Discuss with GTAC (gtac@dh.gsi.gov.uk)*

The map starts from the point at which a decision has been made to generate *de novo* stem cell material. Some stem cell applications will, of course, be developed from pre-existing sources of stem cells, for example, from an embryonic stem cell line accessed from the UK Stem Cell Bank. In such a case, the regulatory route for that particular research programme commences from that point forward on the map.

Feedback on this map can be sent to: gtac@dh.gsi.gov.uk. A more detailed, user-friendly, web-based version is currently being developed and will be available by the end of 2009.

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Key:

Regulatory Question	Research or Manufacturing Activity
Statutory Regulatory Process	Non-Statutory Good Practice

Alphabetical Notes to Accompany this Map

Advanced Therapy Medicinal Product (ATMP): ATMPs are innovative, regenerative therapies which combine aspects of medicine, cell biology, science and engineering for the purpose of regenerating, repairing or replacing damaged tissue/cells. The use of this technology has already led to the development of products that are used clinically for the treatment of burns or ulcers and cartilage repair systems used in the treatment of early arthritis. Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products entered into force on 30 December 2007 and applied from 30 December 2008. The Regulation contains transitional provisions: ATMPs, other than tissue engineered products, which were legally on the Community market in accordance with national or Community legislation on 30 December 2008 will have until 30 December 2011 to comply with the Regulation; & Tissue engineered products which were legally on the Community market in accordance with national or Community legislation on 30 December 2008 will have until 30 December 2012 to comply with the Regulation. In the interim applicants should proceed as previously by contacting the MHRA for classification of a product as a Medicinal Product (MP) or Investigational Medicinal Product (IMP). If a product containing human tissues or cells is not considered an MP or IMP by the MHRA, it will be regulated entirely by the HTA under the Human Tissue (Quality & Safety for Human Application) Regulations 2007 (the 'Quality & Safety Regulations') with regard to procurement, testing, processing, storage, distribution and import / export of the product. The HTA has published guidance and frequently asked questions on their website (http://www.hta.gov.uk/guidance/licensing_guidance/atmp_regulation_and_quality_and_safety_regulations.cfm). Products classified as MPs or IMPs are regulated under the Quality & Safety Regulations only as far as procurement and testing of human tissues and cells are concerned. The MHRA, as the Competent Authority for medicinal products and medical devices, discharges the UK's national responsibilities for ATMPs (e.g. for manufacturing, distribution, clinical trials and pharmacovigilance). The HTA is the UK's Competent Authority under the Quality & Safety Regulations and licenses the procurement, testing, processing, storage, distribution and import/export of tissues and cells for human application. Manufactured products that are classified as medicinal products by the MHRA or European Medicines Agency (EMA) will be regulated under the Quality & Safety Regulations only for the donation, procurement and testing of tissues and cells. The subsequent stages, including manufacture, storage and distribution, will be regulated by the MHRA.

Adverse Event Reporting: Serious adverse event or serious adverse drug reaction or unexpected serious adverse reaction: Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that (a) results in death, (b) is life-threatening, (c) requires hospitalisation or prolongation of existing hospitalisation, (d) results in persistent or significant disability or incapacity, or (e) consists of a congenital anomaly or birth defect. A Sponsor shall ensure that all relevant information about a suspected unexpected serious adverse reaction (SUSAR) which occurs during the course of a clinical trial in the United Kingdom and is fatal or life-threatening is reported as soon as possible to the MHRA, the competent authorities of any EEA State, other than the United Kingdom, in which the trial is being conducted, and the relevant Ethics Committee. This needs to be done not later than seven days after the Sponsor was first aware of the reaction. Any additional relevant information should be sent within eight days of the report. A Sponsor shall ensure that a suspected unexpected serious adverse reaction (SUSAR) which is not fatal or life-threatening is reported as soon as possible, and in any event not later than 15 days after the Sponsor is first aware of the reaction, to the MHRA, the competent authorities of any EEA State, other than the United Kingdom, in which the trial is being conducted and the relevant Ethics Committee. Under the European Union Tissue and Cells Directive, the HTA has set up a system for tissue establishments to report serious adverse events and reactions (http://www.hta.gov.uk/licensing/adverse_event_and_reaction_reporting.cfm). *Serious Adverse Event (SAE)* 'serious adverse event' means any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity. *Serious Adverse Reaction (SAR)* means an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.

Cell Bank: A cell bank system is a system whereby successive batches of a product are manufactured by culture in cells derived from the same master cell bank. Typically a single container from the master bank is cultured to prepare a working cell bank. The cell bank system is validated for a passage level or number of population doublings beyond that achieved during routine production.

European Medicines Evaluation Agency (EMA): The EMA is responsible for the scientific evaluation of applications for European marketing authorisation for medicinal products (centralised procedure). Under the centralised procedure, companies submit a single marketing authorisation application to the EMA. All medicinal products for human and animal use derived from biotechnology and other high technology processes must be approved via the centralised procedure. <http://www.emea.europa.eu/htms/aboutus/emeaoverview.htm>

Genetic Modification (GM): As shown on the interim map, stem cell lines are generated before genetic modification. In the case of induced Pluripotent Stem (iPS) cells, genetic modification will take place prior to the stem cell line being generated. Any centre undertaking GM activities needs to notify HSE. For individual activities, notification is only required where the activity presents a risk to human health or the environment. <http://www.hse.gov.uk/biosafety/gmo/hseandgmos.htm>

Gene Therapy Advisory Committee (GTAC): GTAC is DH supported and has UK-wide responsibility for the ethical oversight of proposals to conduct clinical trials involving cell therapies derived from stem cell lines or gene therapy. GTAC is the UK national research ethics committee (REC) for gene therapy clinical research according to the Medicines for Human Use (Clinical Trials) Regulations 2004. It is the only UK ethics committee empowered to approve clinical trials of gene therapy products according to the definition given in Part IV of Directive 2003/63/EC (amending Directive 2001/83/EC): L159/88 "... [a] gene therapy medicinal product shall mean a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either in vivo or ex vivo, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression in vivo. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell." GTAC is also a recognised REC and wishes to approve clinical trials that use certain gene therapy related products that are not covered under the legal definition above (for instance, antisense applications), as well as cell therapies derived from stem cell lines. Its ethical approval of a clinical trial obviates the need for approval from another REC. <http://www.advisorybodies.doh.gov.uk/genetics/gtac>

Good Laboratory Practice (GLP): Good Laboratory Practice (GLP) embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived. These studies are undertaken to generate data by which the hazards and risks to users, consumers and third parties, including the environment, can be assessed for pharmaceuticals, agrochemicals, veterinary medicines, industrial chemicals, cosmetics, food and feed additives and biocides. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments.

Good Manufacturing Practice (GMP): GMP is that part of quality assurance which ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation (MA) or product specification. GMP is concerned with both production and quality control. GMP inspectors assess manufacturers compliance with the provisions of their manufacturing authorisation and the principles and guidelines for GMP as detailed in the appropriate European Directives. Good Distribution Practice (GDP) inspectors assess Wholesale Dealers' compliance with the provisions of their Wholesale Dealer's licence and the principles and guidelines for GDP. The GMP Inspectorate inspects such companies and their operations to verify their compliance with the EU GMP/GDP guidelines available in Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007 – the 'Orange Guide'.

Health & Safety Executive (HSE): HSE operates and enforces legislation in Great Britain that aims to control the risks to human health and the environment arising from activities involving GM Organisms in containment under the Genetically Modified Organisms (Contained Use) Regulations 2000.

Home Office (HO): The Animals in Scientific Procedures (ASP) Inspectorate provides scientific advice to the Home Secretary and to officials who operate the system that approves licences for laboratories. The breeding and supply of animals for use in scientific procedures is regulated in the UK by the Animals (Scientific Procedures) Act 1986. Proposals to use animals in scientific projects are individually scrutinised. Project licences are only granted when there is no validated alternative to animal tests, the generation of new test data is justified, the protocols proposed cannot be further refined, the protocols will be likely to produce data which will meet the specified objective, All laboratories granted a license must adhere to a strict code of practice which stipulates minimum standards for: animal housing and environment , animal care and health, minimised breeding of surplus animals, humane killing. <http://www.homeoffice.gov.uk/science-research/animal-testing/?version=1>

'Hospital Exemption': Under the Regulations on ATMPs, products which are prepared on a *non routine* basis and used within the same Member State in a *hospital* in accordance with a *medical prescription for an individual patient* will be exempt from the Regulation. Exempted products will need to comply with manufacturing, quality and pharmacovigilance standards which will be defined at national level. The MHRA is currently developing the national arrangements for the UK following a consultation exercise in 2008.

Human Application: In relation to tissues and cells, means use on or in a human recipient, including use in extracorporeal applications, but not including use for autologous graft (tissues and cells removed from and applied in the same person within the same surgical procedure).

Human Tissue Authority (HTA): The HTA is one of the competent authorities responsible for implementation of the European Union Tissues and Cells Directives, which were transposed into UK law via the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (the Quality and Safety Regulations) on 5 July 2007. Under the Quality and Safety Regulations the HTA regulates the procurement, testing, processing, storage, distribution and import/export of tissues and cells for human application. The Quality and Safety Regulations cover England, Wales, Northern Ireland and Scotland. The HTA also regulates the removal, storage, use and disposal of human bodies, organs and tissue for a number of 'Scheduled Purposes' – such as research and education and training – set out in the Human Tissue Act 2004 (HT Act). The HT Act covers England, Wales and Northern Ireland. There is separate legislation in Scotland – the Human Tissue (Scotland) Act 2006. HTA has no remit in regulating embryos. However, when cells are isolated from an embryo and are intended for Human Application, then these cells and tissue are regulated by the HTA. This is contingent on guidance that will be forthcoming from the Committee on Advanced Therapies (CAT) of the EMEA as to what is classified as 'starting material'. The current position is presented in a joint statement with HFEA http://www.hta.gov.uk/guidance/licensing_guidance/position_statement_on_regulating_human_embryonic_stem_cell_lines_for_human_application.cfm

Human Fertilisation and Embryology Authority (HFEA): The HFEA is the independent regulator for in vitro fertilisation (IVF) treatment and embryo research. The HFEA's role is to protect patients and the public interest, to drive improvement in the treatment and research sectors and to provide information to the public and policymakers about treatment and research. HFEA was set up in August 1991 as part of the Human Fertilisation and Embryology Act 1990. The HFEA's principal tasks are to license and monitor clinics that carry out (IVF), donor insemination (DI) and human embryo research. The HFEA also regulates the storage of gametes (eggs and sperm) and embryos. <http://www.hfea.gov.uk/>

Investigational Medicinal Product (IMP): Investigational medicinal product means a pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a clinical trial, and includes a medicinal product which has a marketing authorization but is, for the purposes of the trial (a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorization, (b) used for an indication not included in the summary of product characteristics under the authorization for that product, or (c) used to gain further information about the form of that product as authorised under the authorization.

Master Cell Bank (MCB): A culture of fully characterised cells distributed into containers in a single operation, processed together in such a manner as to ensure uniformity of cellular content of containers and stored in such a manner as to ensure stability.

Medicinal Product (MP): Article 1 of Directive 2001/83/EC as amended defines a "medicinal product" as: "Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis". The MHRA regulates the use of IMPs in clinical trials in the UK – this would include the use of cell lines as a component of an IMP.

Post-Marketing Surveillance: Regulation (EC) No 1394/2007 of the European Parliament and of the Council on Advanced Therapy medicinal products introduces additional provisions to those laid down in Directive 2001/83/EC and Regulation (EC) 726/2004. Article 14 (4) of Regulation (EC) No 1394/2007 specifically requests the European Medicines Agency to draw up detailed guidelines relating to the post authorisation follow-up of efficacy and adverse reactions, and risk management. The EMEA has recently issued this guideline to meet this request and to complement existing guidelines in the area.

Medicines and Healthcare products Regulatory Agency (MHRA): The MHRA is the government agency responsible for ensuring that medicines and medical devices work, and are acceptably safe. No product is risk-free. Underpinning all its work lies robust and fact-based judgements to ensure that the benefits to patients and the public justify the risks. MHRA keep watch over medicines and devices, and take any necessary action to protect the public promptly if there is a problem. <http://www.mhra.gov.uk/index.htm>

Research Ethics Committee (REC): NHS Research Ethics Committees have been established throughout the UK for many years with the purpose of safeguarding the rights, dignity and welfare of people participating in research in the NHS. Potential research participants at any NHS organisation in the UK will come under the protection of a REC. The REC is entirely independent of the researcher and the organisations funding and hosting the research. RECs are recognised by the United Kingdom Ethics Committee Authority (UKECA) for the review of clinical trials of investigational medicinal products (CTIMPs), in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004, for the class of research and geographical area indicated. Recognised RECs (apart from Type 1 Independent Ethics Committees) can also review non-CTIMP research. There are three types of recognised RECs: Type 1 RECs – recognised for review of phase I Clinical Trials of Investigational Medicinal Products (CTIMPs) in healthy volunteers only. Some Type 1 RECs are independent ethics committees (ie non-NHS IECs); Type 2 RECs – recognised for review of Clinical Trials of Investigational Medicinal Products (other than phase I trials in healthy volunteers) taking place within a single domain; Type 3 RECs – recognised for review of Clinical Trials of Investigational Medicinal Products (other than phase I trials in healthy volunteers) and all other research taking place in more than one domain anywhere in the UK. GTAC acts as the specialist REC for gene therapy and certain types of stem cell therapies.

'Specials' Legislation: Medicines legislation (specifically The Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994/SI 3144) requires that medicinal products are licensed before they are marketed in the UK. However, some patients may have special clinical needs that cannot be met by licensed medicinal products. So that these special needs may be met, the law allows manufacture and supply of unlicensed medicinal products (commonly known 'specials') subject to certain conditions. The conditions are that there is a bona fide unsolicited order, the product is formulated in accordance with the requirement of a doctor or dentist registered in the UK, and the product is for use by their individual patients on their direct personal responsibility. If a 'special' is manufactured in the UK, the manufacturer must hold a manufacturer's (specials) licence issued by the MHRA.

Stem Cell Line: A stem cell line comprises cells that can be expanded for prolonged periods in appropriate culture conditions without any change in genotype or phenotype. A diploid cell line would not include cells which have been immortalised following any acquired or induced alteration in genotype. Importantly, phenotypically indistinguishable stem cell lines might have different differentiation capacities. Ideally cell lines should be clonal, that is derived from a single cell. In practice, however, this criterion cannot always be satisfied.

UK Stem Cell Bank Steering Committee: The Steering Committee for the UK Bank and for the Use of Stem Cell Lines must satisfy itself that human embryonic stem cell (hESC) lines used in the UK have been ethically sourced with informed donor consents; are to be used for valuable and ethical research projects reflecting the requirements of the HFEA regulations. The Committee seeks to approve all research with undifferentiated human embryonic stem cells. http://www.mrc.ac.uk/Test/PolicyGuidance_old/EthicsAndGovernance/StemCells/UsingTheUKStemCellBank/MRC003079

Working Cell Bank (WCB): A culture of cells derived from the master cell bank and intended for use in the preparation or production cell cultures.