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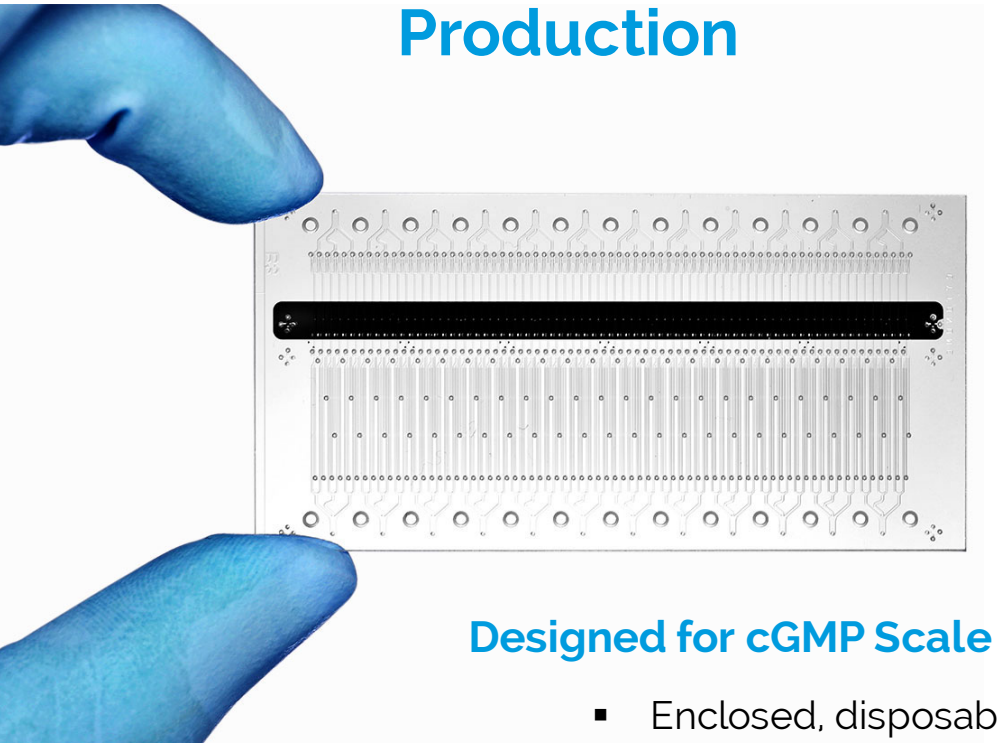

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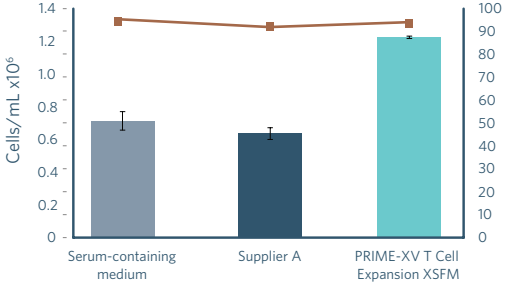

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Regenerative Medicine

The 2016 *Regenerative Medicine* Glossary

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The *Regenerative Medicine* editorial team is delighted to bring you the third edition of the *Regenerative Medicine* Glossary, which we hope will be regarded as an essential resource for everyone who works in regenerative medicine.

This guide will be particularly useful for both experts and newcomers within academic, clinical, industry and societal settings. Importantly, this glossary will aid in harmonization of the terminology used in the regenerative medicine community within and between companies, universities and individuals. With increased globalization in stem cell and regenerative therapies, it is now more important than ever before that scientists speak the same language.

This year we bring an updated version with new definitions provided from experts in the field. Susan Solomon and Michael Yaffe (NYCSF, NY, USA), Jon Rowley (RoosterBio, MD, USA), Alain Vertès (NxR Biotechnologies, Basel, CH) and Alicia Henn (BioSpherix, NY, USA) have been working closely with the *Regenerative Medicine* editorial team over several months to develop this new glossary.

For completeness, we have republished the definitions of the previous version, curated by The British Standards Institution in 2012 [1], which remain relevant to this day. The expert panel includes definitions that have come to the forefront in recent years. Some key examples include 'stem cell tourism', 'mitochondrial replacement' and 'CRISPR/Cas' – terms which have been the topic of much discussion and sometimes controversy.

Furthermore, this glossary features exclusive editorials on current topics in regenerative medicine, written by the members of our expert panel. Susan Solomon and Michael Yaffe offer a piece on the influence of stem cell advocates who have been the driving force in funding and development of stem cell-based therapies [2]. Jon Rowley *et al.* discuss emerging trends in stem cell therapy manufacturing and the valuable lessons that could be learned from cell expansion technologies in the protein bioprocessing industry [3]. The current and upcoming trends and developments of cell-based therapies are then discussed in a piece by Alain Vertès [4] and finally, in her editorial, Alicia Henn discusses the importance of biosafety in regenerative medicine research [5].

This glossary concisely defines core established regenerative medicine terminology, as well as recently introduced language that has now become

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commonplace. It is our intention that this glossary will be updated when required to allow for the inclusion of new terms and to incorporate any changes to definitions. In this vein, we welcome your feedback and suggestions for future editions.

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Susan L Solomon is Founder and Chief Executive Officer of The New York Stem Cell Foundation (NYSCF) Research Institute, the world's leading non-profit research institute dedicated to translating cutting-edge stem cell research into clinical breakthroughs. Privately funded, NYSCF is unconstrained and therefore unique in its ability to expedite the most promising stem cell research both at its own independent laboratory employing 45 full-time scientists and through its collaborations with more than 50 academic, philanthropic, and corporate institutions around the globe. In addition, NYSCF has built a community of over 140 leading stem cell scientists internationally. From a standing start in 2005, NYSCF has raised and invested more than $160 million in 'tipping point' stem cell research, accelerating progress in finding treatments and cures for diabetes, ALS, multiple sclerosis, Parkinson's, Alzheimer's, heart disease, cancer, schizophrenia, bone injury, and macular degeneration, among other diseases.

A lawyer by training and a chief executive and entrepreneur by experience, Ms. Solomon has decades of leadership experience in starting and building effective and focused organizations. Ms. Solomon started her career as an attorney at Debevoise & Plimpton, then held executive positions at MacAndrews and Forbes and APAX (formerly MMG Patricof and Co.). She was the founder and President of Sony Worldwide Networks, the Chairman and CEO of Lancit Media Productions, an Emmy award-winning television production company, and then served as the founding CEO of Sothebys.com, prior to starting her own strategic management consulting firm Solomon Partners LLC in 2000.

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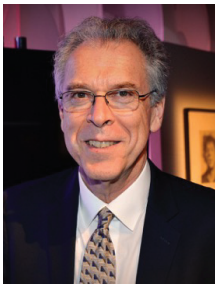

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Michael Yaffe is the Vice President of Scientific Programs at the New York Stem Cell Foundation (NYSCF) where he oversees granting activities and works to expand collaborative research programs. He was previously Associate Director of Research Activities at the California Institute for Regenerative Medicine (CIRM) where he led the Basic Biology team, designed funding programs and monitored research progress. Michael is Professor Emeritus and was on the faculty at the University of California, San Diego (UCSD) for 23 years. His laboratory studied cell growth and subcellular structure, with particular focus on the mitochondria, the cellular power plants. His research utilized biochemical, genetic and microscopic approaches. He also taught both undergraduates and graduate students and served for 3 years as Associate Dean for Education in Biological Sciences. Michael has served on grant review panels for the NIH and the American Cancer Society and as an organizer for a number of international scientific conferences.

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Jon A Rowley, PhD, is the Chief Executive and Technical Officer of RoosterBio Inc. Jon started RoosterBio in 2013 as part of his personal quest of having the biggest impact possible on the commercial translation of technologies that incorporate living cells, including cellular therapies, engineered tissues, and tomorrow's medical devices. Jon holds a PhD from the University of Michigan in Biomedical Engineering and has authored over 30 peer reviewed manuscripts and 20 issued or pending patents related to biomaterials development, tissue engineering, and cellular therapy. Jon started his industry career at BD as a scientist and R&D manager in a Cell & Tissue Technologies group focused on applying high-throughput screening technologies to cell therapy media development and tissue engineering. Jon then contributed to the clinical development of Aastrom Biosciences' Tissue Repair Cell product. Jon most recently spent 5 years as Director of Innovation and Process Development in Lonza's Cell Therapy CMO business, and currently resides in Walkersville, MD with his wonderful wife and their 3 young children.

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Dr Alain Vertès is Managing Director at NxR Biotechnologies, a boutique consulting firm based in Basel, Switzerland.

Dr Vertès came to this role after extensive experience in the pharmaceutical and industrial biotechnology sectors, in Europe, North America, and Asia in different functions including research, manufacturing, partnering and sales, in pharmaceuticals (Lilly, Pfizer, Roche), petrochemicals (Mitsubishi Chemical Corporation), public research (Institut Pasteur; RITE/Kyoto), contract research (Battelle Memorial Institute, PPD) and consulting (Australian Strategic Policy Institute). Focusing on innovation commercialization, he was a key player in the evaluation, selection, deal making, implementation, and alliance management of novel products and emerging technologies. For example, he championed radical innovation for bringing to patients disease-modifying, paradigm-changing therapeutics such as siRNA (Scrip Award 2008).

Dr Vertès received an MSc degree from the University of Illinois at Urbana-Champaign, a PhD from the University of Lille Flandres Artois, and is a Sloan Fellow from London Business School (MBA/MSc).

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Dr Henn holds an MBA from University of Rochester as well as a PhD in Molecular Pharmacology and Cancer Therapeutics from Roswell Park Cancer Institute in Buffalo, NY, USA. She has conducted research in industry for Vaccinex, LLC, and in academia at the Center for Biodefense Immune Modeling at the University of Rochester. An inventor with patents for novel methodologies and technologies, Dr Henn is the owner of the *In Vitro* Reproducibility group on LinkedIn. She joined BioSpherix as Chief Scientific Officer in 2013. There, Dr Henn directs all scientific programs, writes the company blog, and presents physiologically relevant oxygen research at stem cell and regenerative medicine conferences around the world.

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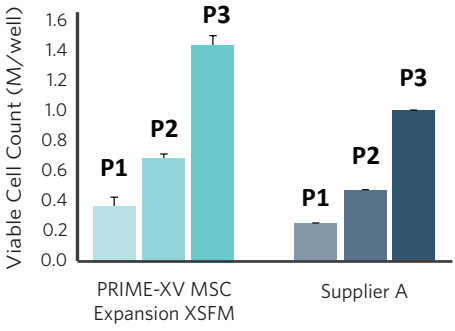

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Regenerative Medicine

Renewing our attention to the patient's voice

Keywords: advocacy • patients • patient advocates • regenerative medicine • stem cells

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Patients and patient advocates have provided a critical impetus to fund and drive stem cell biology and the development of stem cell-based therapies. As this young field developed, the influence of these advocates came at a critical time when an absence of federal funding by the US government hindered groundbreaking research on human pluripotent stem cells. This advocacy, together with support of key members of the scientific community, led to a number of state and local efforts including, notably, establishment of the California Institute for Regenerative Medicine (CIRM), a funding agency of the State of California, and the New York Stem Cell Foundation (NYSCF), an independent, philanthropically supported organization that both performs research in house and supports young stem cell researchers worldwide [1–3]. These groups, along with a number of disease foundations and scientific organizations such as the International Society for Stem Cell Research (ISSCR), have played key roles in supporting stem cell research, bringing new scientists into the field and advancing stem cell technologies.

Over the past 10 years, remarkable progress has been made in understanding stem cell biology and using stem cells to model human disease [4–7]. The pace of this work continues to accelerate with transformational advances in reprogramming technology, genomic modification of cell lines and the development of differentiation protocols for generation of a variety of functional cell types [8–11]. Increasingly, stem cell research is enabling translational studies and the development of novel cell- or drug-based therapies for diverse diseases and injuries.

Both despite and because of this impressive recent research progress, we still need the patient's voice to encourage and inform therapy development. Patient advocacy confers a relevancy, instills a sense of urgency and provides a *raison d'être* for much stem cell research. And as efforts of many groups move increasingly toward translation and the development of novel therapies, the need for patients' inputs becomes all the more essential. Patients and their advocates can provide distinctive perspectives on a potential therapy's practicality, tolerability, cost–benefit considerations

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and competitiveness with existing treatments. They can supply support for and needed pressure on researchers, drug developers, program managers, politicians and regulators to maintain priorities and accelerate activities that will bring novel therapies into the clinic.

Patients bring a unique and critical perspective that can frame and focus research plans and individual experiments. They may communicate to scientists subtle aspects of their disease that may help stratify patient populations and can inform novel treatment strategies. Such advice and involvement in research can accelerate progress. For example, the robust participation of patient advocates in the NIH Rare Diseases Clinical Research Network (RDCRN) helps facilitate diverse research consortia programs, aids study design and patient recruitment, and energetically supports the productivity of research collaborations [12]. Others have recently described how patient input in drug development can help provide fresh outlooks on disease burden, trial design and evaluation of treatment impact [13].

Informed patient advocates can serve also as scientific ambassadors, communicating and explaining complex research and the scientific process to patient groups and the broader community. They can mobilize government and private support for science and can encourage regulatory bodies to act expeditiously and responsibly. Their advocacy can expand public support for science and lead to more rapid acceptance of medical innovation.

Stem cell researchers can benefit greatly from listening to the patient's voice. Patients bring unique insights that can strengthen the quality and impact of disease research, bolstering efforts to understand disease mechanisms, identify therapeutic targets and devise new strategies for tissue repair or replacement. These cooperative partnerships will accelerate the development of novel therapies to cure the major diseases of our time..

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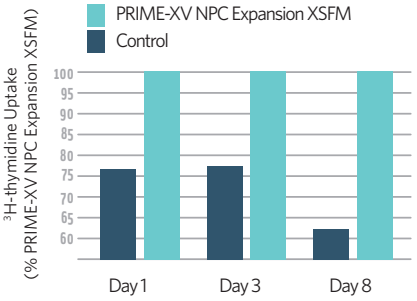

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Scaling up: how manufacturing sciences will dictate the future of cell therapy

Keywords: bioprocessing • cell manufacturing • cell therapy

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New applications for stem cell therapies are being developed at a rapid pace in order to meet the growing patient population seeking treatment for a wide range of diseases and medical conditions. Currently, there are over 56 million people receiving Medicare (over age 65 years) and the Department of Veterans Affairs estimates that it treats 8.76 million veterans each year, and this number is expected to grow as more veterans seek treatment returning home from battle [1,2]. On the clinical side, it was reported in August 2016 that there are 546 registered clinical trials utilizing human mesenchymal stem cells (hMSCs) alone, which is more than a fourfold expansion of trials reported in 2011 [3,4]. By a large margin, hMSCs are the most utilized cell type in research today. This cell type is attractive for use in cell therapies due to their availability, versatility and capability to differentiate and respond to environments with beneficial trophic, immunomodulatory and anti-inflammatory effects [5,6]. The uses of stem cells for treatment include cell engraftment for replacement of damaged tissue, and by injection for regulation of bioactive factors with therapeutic effects, both of which require high cell doses ranging from 10^5 to 10^9 cells per treatment [7].

Traditional technology platforms currently used for stem cell expansion are challenged by their scalability, and manufacturing lots are limited to hundreds of millions to billions of cells [8]. As therapies move quickly from Phase I to Phase II and III clinical trials, therapeutic companies are required to demonstrate the feasibility of a consistent and reproducible manufacturing platform that can provide sufficient quantities of cells for commercialization, often in the range of 10^{12} and 10^{13} cells per lot. Relatively new fields, such as cell therapy, can often borrow best practices from related industries, and in this case, cell expansion technology developed based on the protein bioprocessing industry.

From the bioprocessing perspective, cells are just another biological material requiring isolation, purification and concentrating. However, new challenges arise in cell therapy where cells are the final product that cannot be filter-sterilized, unlike in protein bioprocessing. Hence, a high level of sterility, cell viability and functional capacity is required for cells coming out of the bioprocess. Effectively expanding

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hMSCs to commercially relevant lot sizes at an economical cost while maintaining cell phenotype, function and purity requires significant development in manufacturing sciences. This must be accomplished by producing cells with GMP-compatible raw materials, highly efficient media systems, new culture methods and possibly a combination of different feed regimes such as batch, fed-batch or perfusion systems. Such advances to current hMSC culture practice will drastically reduce total labor hours and media cost, a significant factor in final cost of goods (CoGs), which will reduce the total cost on a per cell basis [9]. New product configurations, such as off the shelf products, standardized raw materials, and plug and play systems, will contribute a significant role in allowing for rapid technology transfer from the lab to large-scale manufacturing processes. These innovations within manufacturing sciences will help to reduce the time and cost it takes to bring a lab discovery to the clinical trial stages, and ultimately to the patients in need.

Technology companies are quickly developing products for the scale-up and processing of hMSCs, based on market demand, which in turn will provide better tools for researchers to progress. Pre-sterilized and ready-to-use microcarriers are effective tools for greatly increasing the surface area for hMSCs to attach and grow on for large volume cultures, while reducing the footprint required for the bioprocess. The microcarrier systems for culturing adherent hMSCs are now offered in bottles, but more importantly, in closed-system bags, pre-sterilized and ready to seed into a bioreactor system [10–12]. Microcarriers in the past had to be prepared and autoclaved by the end user, creating work and yet another set of variables to control when adapting this technology. By providing irradiated microcarriers that are quality controlled for efficient cell attachment, this takes one more processing step out of the hands of the process development scientist and makes implementation much simpler.

Recent studies have shown that hMSCs cultured in microcarrier suspension processes are reaching a new level of cell density, north of 1 million cells/ml, and up to 3 million cells/ml in a serum containing media [13]. These numbers are tenfold greater than any number published or presented just 5 years ago, and the highest and most consistent observed to date. Achieving this cell density is attributed to microcarrier/media combination, low shear bioreactor design, and good bioprocess engineering – all three of which are critical for scaling up to the volumes of cells that will be required for bringing cell therapies to the industrial scale. This technology represents a significant achievement in that it demonstrates that the numbers of cells required for commercial production (trillions of cells) is feasible with the use of thousand-liter bioreactors. The next step is to evaluate the economics of such bioprocessing methods and their impact on the control the cost of goods (CoGs) of the final product.

Vendors are also beginning to focus on the post-expansion/downstream processing (microcarrier removal, cell concentration) of the cells, as delivered by the high cell volume in upstream processes. Systems for microcarrier removal and cell concentration using depth filtration, mesh bags, alternating tangential flow (ATF) technology and continuous centrifugation technologies are being developed and optimized to reach high post-processing cell viability and recovery [12,14]. Downstream processing continues to be an underappreciated aspect of the field and should not be an afterthought to scale-up culture. If a cell expansion is scaled to several hundred liters before strategies for processing massive cell volumes are developed, it could set the process development back, in excess of a year, while these technologies are established and integrated into the manufacturing process.

Innovation drives disruptions in current standards of practice and there are several on the horizon in the cell therapy field aimed

at simplifying product development, reducing production times, eliminating risks in manufacturing processes and driving down cost. While the technology innovation is progressing rapidly, there is a need in the cell bioprocessing field to establish standard measurement metrics. The primary protein productivity metric is g/l, or grams of protein produced per liter of media consumed. On the cell therapy side, we are at a point of achieving highly concentrated and large volume batches of cells, warranting a new cell productivity metric – millions of cells per liter (M cells/l). This metric outlines the technological and economic aspects of the bioprocess in terms of cell yield per media consumed. This key metric will be important for the industry to adopt as it provides fundamental goals for achieving an economic bioprocess, allows for direct comparisons across technology platforms, and tracks upstream bioprocess improvements over time. More importantly, the CoGs of products can be derived when such measurement metrics are used for evaluating the economics of the bioprocessing platform.

As with any developing technology, receiving ample funding and attention from federal agencies for the proper development is difficult to come by, and this has been the case for the manufacturing sciences field of regenerative medicine. In order to maintain our innovation edge in this growing industry, an industry–academic consortium was created in 2014 that laid out the technology roadmap for scalable and cost effective manufacturing of living cell-based products through the year 2025. The aim of this Cell Manufacturing Consortium, developed through the National Institute of Standards and Technology, is to promote the advancement of cell manufacturing technologies by developing partnerships between public and private industry and academic members, with the thought that their collaboration will ease the translation of new cell therapies to the market [15]. This is laying the groundwork for several agencies to fund groundbreaking cell manufacturing projects, estimated to be in the tens to hundreds of millions of dollars, over the next several years. This funding will allow for the technological and developmental work required to create economic and sustainable commercial manufacturing of therapeutic cells. Public and private funding in manufacturing sciences will be critical for bridging the technology gap between basic discoveries and commercialization of safe and effective cell-based regenerative therapies.

Taken together, these developing trends in the manufacturing of stem cells are laying the groundwork for the future of cell therapy. The immediate priority is to establish working relationships between stem cell scientists in research and industry, with those skilled in the up-scaled manufacturing and downstream processing of biologics in the industry. When this is established, it's anticipated that there will be great technological innovations in the cell therapy field that will warrant further funding from federal agencies. We are on the dawn of a new age in regenerative medicine and it will be powered by the stem cell manufacturing revolution.

Financial & competing interests disclosure

TR Olsen and LT Lock are employees of RoosterBio Inc. JA Rowley is the Chief Executive Officer of RoosterBio Inc. and maintains ownership. RoosterBio Inc. is a human stem cell manufacturing company focused on accelerating the cell-based bioeconomy by providing standardized stem cell product platforms that enable rapid clinical and commercial translations. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Supplement

Regenerative Medicine

Innovation S-curves of cell-based therapies

Keywords: CAR-T cells • cell-based therapeutics • endogenous stem cells • gene-based therapeutics • genetic engineering • HSCs • MSCs • pluripotent stem cells • radical innovation • regenerative medicine • S-curve • technology adoption

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Innovation proceeds in S-curves [1]. Such patterns are well documented in historic accounts of the emergence of technology platform-to-products companies in virtually all industries. In the arena of monoclonal antibodies (mAbs), these companies comprise Genentech, Amgen, Centocor or Biogen; the main technology S-curves there progressing from murine antibodies (1980s), to chimeric antibodies (late 1980s), fully human antibodies (2000s), antibody fragments (late 1990s–2000s), and further on to multivalent antibodies, immunotoxins and synthetic antibodies (2010s and beyond) [1]. Integrated, these discrete S-curves, or 'innovation chunks', constitute the three-decade long aggregate mAb innovation S-curve. The tipping point here was the capacity to 'humanize' antibodies to overcome anti-idiotypic foreign body HAMA responses. Despite the technology of cell therapeutics still being in its infancy, several technology S-curves that will mark the development of cell-based therapies can already be identified [1]:

- The therapeutic use of various cell types including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), pluripotent stem cells and their derivatives, T cells or NK cells and their engineered derivatives (e.g., CAR-T cells or CAR-NK cells), dendritic cells;
- Manufacturing;
- Enhancement of biological attributes;
- Combination with conventional drugs;
- Formulation;
- Delivery devices;
- Solid organ transplantation.

The deployment of successful radical innovations that bring paradigm-changing products to the market has dramatic positive impacts on financial indicators. Taking again the example of mAbs, F. Hoffmann La Roche (Roche) took a controlling equity stake in Genentech in 1990; a decade later, the worldwide sales of the blockbuster Mabthera (rituximab)

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exceeded in 2001 CHF 1 billion, and CHF 4 billion in 2005. This success significantly contributed to Roche's operating profit that grew by 25.4% in 2005 from 16.3% in 2001, with the Roche oncology sales growing 40% in 2005 and total sales 25%, as compared with 17% for the oncology market as a whole [2]. In 2008, the market share for mAbs was estimated at US$33 billion, and Roche's share at $15 billion [3]. The market equivalent of Genentech's value at the time of Roche's full acquisition in 2009 was $64 billion [4].

Radical innovation oftentimes echoes creative destruction. This phenomenon can be ascribed to a dependence on a single technology, thus resulting in a 'black swan' risk, that is, the risk for an unlikely but highly disruptive event to occur (here, the coming of age of a radical innovation). In the absence of a suitable hedge, for example another technology platform at steady-state, or a quick turnaround to adapt to the new business reality, black swan technology events typically result in a dwindling business and eventually in bankruptcy.

Since the 1990s, competitive success originates from building and dominating fundamentally new markets. Personalized or precision medicine real options in conventional therapeutics offer pharmaceutical companies business growth paths that might be rewarding enough and optically less risky than the adoption of radical innovation such as mAbs in the 1990s, or nowadays cell-based and gene-based therapies. Large firms in any industry have a tendency to favor investment in projects that represent incremental deviations from the status quo [5]. Large pharmaceutical firms favor investment in projects with incremental deviations in small molecules or conventional biologics. Given this tendency to not invest in high risk (but potentially high reward) radical innovation and their lack of cultural agility against technology disruption risk, a question is why large pharmaceutical companies do not fail more often?

An element of response is that these companies exploit evergreen technology platforms (e.g., small molecules) and operate a number of different franchises, thereby spreading risk. As a result, if a pharmaceutical company does not invest early in a radical innovation that will subsequently prove successful, it merely runs the risk of a decreased ranking and the need to reorganize or implement an M&A depending on its cash reserves, but will still have some opportunity to jump in the bandwagon in the form of product in-licensing or partnerships, as was the case with the late mAbs adopters. Furthermore, these companies have mastered product cycle management and nowadays divest R&D-stage or marketed compounds more than ever before.

Pharmaceutical companies still delay large-scale investments in cell-based and gene-based therapies, given remaining technological and market risks [6]. This slow rate of adoption, and sometimes U-turns after investing, constitutes a vexing hurdle as big pharmas with their exquisite core competences in incremental innovation and broad sales network offer the industry key elements of the innovation ecosystem. Nevertheless, all closely monitor progress, or conduct clinical development programs, in advanced therapeutic medicinal products, as exemplified by GSK to build with the HSC-based Strimvelis new competence factors and infrastructures [6,7], or Novartis with CD19-CAR-T cells-based tisagenlecleucel-T [8,9]. Furthermore, several regenerative medicine strategic alliances transactions have already been implemented [6]. The greatest difficulty is perhaps that the regenerative medicine industry is currently only approaching the point of inflexion of its first generation S-curves [10,11].

Breaking barriers to accelerate the pace of regenerative medicine is what has been achieved by Japan's 2014 PMDA Act [12]. This regulatory change provided an accelerated conditional approval path for regenerative medicines that are demonstrated in humans to be well tolerated and for which indications of efficacy have been generated. It has triggered a translational momentum in Japan, with Japanese pharmaceutical firms having been the most active at implementing cell-based therapy partnerships, while foreign companies are prioritizing Japan in their developmental efforts [4,6,12]. Similar evolutions are being considered elsewhere, for example in the USA (the REGROW Act) and in South Korea [7].

A hybrid design at the interface of cell-based/gene-based therapies and therapeutic mAbs, is the technology of CAR-T cells. Building on the magic bullet immunotoxin concept of linking a toxin to a functional delivery group, a targeting antibody is linked to a T cell to combine the specificity of the antibody with the T cell function. The first double-chain chimeric antibody receptor was constructed in 1989; pilot clinical trials using an improved architecture showed the first complete remission of cancer patients in 2008 [8,13]. Several major roadblocks nevertheless remain, including that approximately 30% of the recipients of the new adoptive therapy are at risk of developing very severe cytokine-release syndromes, the intensity of which has been observed to be linked to the tumor burden at the time of treatment [14,15]. Moreover, there are business model issues when autologous cells are used, resulting in the new therapy having a large and costly service-based component. Complex also are the pricing and reimbursement issues generated by the change of paradigm, from symptomatic or disease-modifying to high-cost curative medicines. Future innovation chunks in CAR-T cell development include:

- Enhanced safety (on/off molecular switches, suicide switches, antidotes);
- Universal T cells (both allogeneic CAR-T cells and universal 'lego-like' CAR-T cells for treating different cancers);
- Enhanced specificity and selectivity;
- Enhanced efficacy (armored CARs, combination therapy e.g., with checkpoint inhibitors);
- Enhanced persistence and relapse prevention;
- Improved manufacturing;
- Treatment simplicity and speed;
- Improved logistics;
- Biomarkers;
- Combination therapies.

The second wave of innovation here needs to progress from the safe treatment of liquid cancers to the treatment of solid cancers. As a result, and given the large market potential, the level of adoption of CAR-T cell therapies is unparalleled amongst cell-based/gene-based therapeutic platforms [16].

Innovation chunks can be forecasted for other cell-based therapies. For example, HSCs transplantation can now be contemplated for the delivery of genetically engineered HSCs as curative treatment for severe genetic diseases of the blood, and even AIDS [17,18]. Moreover, allogeneic MSCs have been proven to be well tolerated in hundreds of independent clinical trials involving thousands of patients, with products already approved in several jurisdictions exemplified by remestemcel-L [17]. The inflexion point of the aggregate MSC innovation S-curve undoubtedly lies with enhanced efficacy taylor-designed to the indication of interest [1,17]:

- Using alternative manufacturing methods;

- Licensing of MSCs for adoptive therapy or recruitment of endogenous MSCs;
- Altered cell surface ligands to promote homing, novel MSC subtypes;
- Multiple mechanisms of action using genetically engineered MSCs;
- Cell–cell combination therapies;
- Cell–biologics combination therapies;
- Cell–small molecule combination therapies;
- Biomarkers.

Regarding pluripotent stem cell-derived products, novel treatments for metabolic diseases or for ocular diseases are likely to be commercialized first.

Putting all these perspectives together, the regenerative medicine industry is currently in a period of transition: the first-generation cell-based therapies as a whole is fast approaching the market. Regulatory approvals will increasingly drive big pharmas to adopt the new technology as the opportunity cost with conventional pharmaceutical modalities decreases. Moreover, the next wave, that is, genetically engineered cell-based therapies, including CAR-T cells, is already in progress. Nonetheless, a large technology risk remains, but the more mature MSC- and HSC-based products are poised to crystallize interest for and adoption of these emerging technologies. Last but not least, recent advances in developmental biology and stem cell biology makes more attractive than ever before the use of chemistry, a core competence of pharmaceutical companies, for drugging endogenous repair mechanisms leveraging for example endogenous pericytes/MSCs in the cardiac, inflammation or orthopedics disease areas, akin to the blocking of negative immune modulators to unleash the cancer-fighting potential of T cells [19,20].

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Supplement

Regenerative Medicine

Protecting our people: the evolution of biosafety and regenerative medicine

Keywords: biocontainment • bioprinter • biosafety • infectious aerosols • laboratory-acquired infection

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The environment for the laboratory worker has changed considerably since 1938 when Alexis Carrel and Charles Lindberg published 'The culture of organs' [1]. With all of the improvements in laboratory safety since then, most laboratory workers report feeling safe at work, yet almost half have experienced a laboratory injury or exposure [2]. There is an urgent need for the improvement of biosafety, particularly in the emerging field of regenerative medicine.

In the 20th century, biosafety was a moving target. As infectious agents were identified in the laboratory, reports of matching laboratory-acquired infections (LAI) kept pace [3]. People have been injured [4], and killed in laboratory incidents [5]. One lethal incident resulted in criminal charges against a research institution and a primary investigator [6]. Outbreaks of infectious disease have even spread beyond the lab to workers' families [7,8]. Due to experiences with lapsed biocontainment the current recommendations are to process human tissue samples in a biosafety hood [9,10]. With use of modern equipment, today's cell and tissue handling laboratory is a much safer place than it used to be.

However, even with modern laboratories, LAIs still occur every year [11]. There are many disincentives for hands-on workers, PIs and institutions to report LAIs, so it is generally accepted that there are many more infections and vastly more exposures than are reported [12]. From an ethical point of view, it is absolutely critical that we protect our workers.

Potential routes of transmission of LAIs have been separated into five categories: oral ingestion, animal bites or scratches, parenteral inoculation by needles or other sharps, spills or splashes onto skin and mucous membranes, and inhalation of aerosols. Combined, the first four routes account for only 20% of infections reported. However, only about 50% of cases reported had obvious probable routes of transmission reported at all. In the rest of the cases, no route of transmission was apparent [9].

Biological materials are separated into four levels based on their relative risks to workers such as infectivity of potential agents and the availability of treatments [9]. Biosafety

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Level One (BSL-1) materials are generally approved for handling in room air. BSL-2 materials encompass all samples with some known risks such as human patient samples that present an obvious risk by ingestion, injection or mucous membrane exposure. BSL-3 include samples with known inhalation risks for which there are available treatments, and BSL-4 level is reserved for samples with particularly high risks, such as newly emergent viruses, for which there are no known treatments.

Most research laboratory work on primary human cells is carried out at a BSL-2 or 2+ level. Biohazard signs are posted outside of the lab and engineering controls such as the biological safety cabinet are used to help prevent infection. No eating, drinking, applying make-up or smoking is permitted. Contaminated materials are decontaminated with chemicals and/or the autoclave and handled as biohazard waste. Laboratory safety programs generally include routine use of personal protective equipment (PPE) such as gloves, lab coats, and eye protection.

That doesn't necessarily mean that these practices are strictly followed in every laboratory. There have been calls for a major change in the culture of laboratory safety so that from the top-down laboratory workers take biosafety seriously [12,13]. 'Biorisk' is a new term encompassing biosafety, biocontainment and biosecurity in the laboratory. Following major recent microbiological laboratory biosafety lapses in the US federal laboratories, the NIH updated its biorisk management policies [14] and the White House has released new recommendations to achieve 'a laboratory culture of responsible conduct'.

When no route of LAI transmission is obvious, the causative agent is assumed to be carried by unseen aerosols [9]. These tiny droplets present a unique hazard in the biological or clinical laboratory. They are easily generated during routine cell handling. Small aerosols remain airborne and can travel throughout the room unseen, a hazard to anybody breathing there.

Any procedure that adds energy to liquid-containing samples is potentially aerosol-generating. One laboratory worker was infected with scrub typhus after sonicating a cell sample [15]. Another lab worker in Germany seroconverted to HIV positive after a droplet of serum flew into his eye as he uncapped a tube [16]. Pipetting, vortexing, stirring, shaking, thawing, even dicing biological materials should be considered activities that put biohazardous droplets into the air. These aerosols are not obvious to the worker generating them, nor to others that happen to be in the room.

The biological safety cabinet (BSC) was introduced into widespread use to contain airborne biological hazards. However, even when using a BSC, exposures can still occur. The laminar air curtain at the front of the BSC is easily disrupted by objects carelessly placed over the vents or even by the operator's arms. The proximity of small infectious particles to the worker's face during BSC air breaches makes transmission more likely. Larger airborne infectious particles can settle invisibly on the gloves and sleeves of laboratory workers, to get carried to the mucus membranes by touch [9]. Cell phone use in the laboratory has introduced potent new hazards, with the increased risk of transmission of infectious particles from the PPE to the face.

Even with modern BSC use, in the past year, at least two cases of LAIs have been reported widely. In one case, an Italian technician with no apparent puncture wounds became infected with the strain of HIV with which he was working [17], reminiscent of the HIV-transmitting serum droplet incident in Germany [16]. Another laboratory worker became infected with *Salmonella* in a

place that should have the tightest biosafety practices, the US Centers for Disease Control [18]. In these cases, all the proper processes were followed and there was no apparent route of transmission, which makes aerosols the most likely culprit.

There are several factors that raise the specific biosafety risk of regenerative medicine research and tissue production. The likelihood of use of human tissues adds one biohazard risk factor to the regenerative medicine laboratory worker. Whether allogeneic or autologous, human tissues are the source of the cells, and human cells and tissues will be the final products. This raises the risk of infectivity of any materials in use to human workers. Added to the infection risk of using human cells, the unknown risks of powerful new gene editing techniques such as CRISPR/Cas systems, has made the need for biocontainment of infectious aerosols more urgent.

Particles generated by equipment used in developing novel human cell and tissue treatments add another risk factor to the regenerative medicine laboratory. The high rate of generation of particles by cell sorters, often used in the first or the final selection step with human cells, is a biohazard risk, particularly when the sorter nozzles clog. Aerosol containment systems have been put into place by the manufacturers of cell sorters to try to reduce these hazards. Even with aerosol containment systems, sorters are often placed inside huge BSCs to try to reduce biohazard risks even further. However, none of these protect the sorter operator that throws open the containment system and sticks their head in to get a closer look.

Bioprinters, at the heart of some of the most novel tissue therapies, are a particularly rich source of biohazardous aerosols. They can generate up to 20 billion particles per minute [19]. However, even in the face of this obvious danger, bioprinters are often used on the open bench, outside of even the containment that a BSC can provide.

Routine laboratory work presents persistent hazards. In the face of daily risk, it is easy for confidence in cell and tissue processing to turn into complacency. Human factors come into play when trying to prevent all kinds of workplace dangers [20]. To prevent human failures by hands-on staff from becoming disastrous, safety measures must be put in place by upper management.

Any barrier that is put into place between the cells or tissues and the humans handling them, increases the biosafety of the operations being performed. Many manufacturers are now designing their bioprinters to be small enough to fit into a standard BSC. However, there are all the same risks that go with all BSC use inherent in this arrangement. Manufacturers of some larger bioprinters are now providing large enclosures around their printers to try to mitigate aerosol risks. However, these static enclosures do not actively filter out potentially infectious aerosols, just limit their spread.

As we move into the future, closed processing systems with active containment measures offer more comprehensive biosafety controls for regenerative medicine. Closed aseptic containment isolators actively remove infectious aerosols and particles through HEPA filtration, while monitoring and recording the internal environment. These can be used not only to provide biosafety protection, but to help document it.

Stepping forward into this new field with all of its promise, we need to adequately address its risks to our people as well. In keeping our laboratory workers safe from LAIs, upper management also may be protecting their families and our broader communities

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1. NEW TERMS & DEFINITIONS

1 additive manufacturing

the patterning and construction of an object from a digital design by sequential deposition and annealing of smaller units of material such a strings or beads

2 animal-free (or xeno-free)

a product that does not contain, or a process that is not conducted with, any animal-derived raw material

3 batch culture

a culture method used to grow cells with an initial, limited, and defined supply of nutrients for a duration of time where the culture media is not replaced throughout the process

4 bioassembly

the automated construction of organs from macroscopic structures containing living cells

5 Biofabrication

1. the construction of 3D objects by living organisms, such as pearls
2. the construction of a three-dimensional object with a biological function
3. the patterning and construction of a living tissue from a digital design by sequential deposition and annealing of smaller units of living material such as cells, or aggregates of cells, usually within a cell-enclosing matrix. Can include **Bioprinting** and **Bioassembly**

Note: Maturation of the construct is usually needed before a biofabricated organ can function so that cells in adjacent deposited units can bind one another and reorder themselves into a more complex tissue

6 bioink

bioprinting-ready material composed of cells, matrix materials, or a combination of both with properties that allow for the fabrication of three-dimensional (3D) cell-based and tissue based constructs

7 bioprinting

manufacturing technology that uses three-dimensional (3D) printing machineries to align, pattern, and build cell-based and tissue-based constructs based on a computer aided designed 3D drawing

8 bioprocess development

A technical discipline utilizing design, engineering, and optimization approaches to develop scalable and economical processes for manufacturing of cellular-based or tissue-based biological products

9 CAR-T cells

Chimeric Antigen Receptor T cell: a T cell that has been engineered to express at its extracellular surface an artificial antigen receptor for example against a certain type of cancer or virus (initially also referred to as T-body)

10 cost of goods sold (CoGS or COGS)

the costs to make and sell a particular product, for example, all the costs to safely manufacture, test, document, store, and transport a therapeutic cell dose, tissue, or organ. These costs must be minimized to get therapeutics to the market.

11 cytotherapy (cytotherapeutic)

a human or veterinary treatment (product) that comprises a live cell-based material (see: cell-based therapy)

12 CRISPR/Cas

a biotechnology tool, utilizing components of a prokaryotic immune system, for making highly specific genomic modifications

13 cytocentric

putting the cells' needs first, creating a full-time physiologically relevant *in vitro* environment for cells, tissues, and organs that is protected from the variability and risks of room air

Note: Most often used in an industrial setting to refer to objects rendered in plastics or other non-biologic materials

14 disease-in-a-dish

a human disease model comprised of cultured cells displaying properties of diseased tissue

Note: many such models are generated using cells differentiated from iPSCs derived from individuals with a specific disease

15 embryo-safe technique

technique to derive embryonic or embryonic-like pluripotent stem cells without the destruction of an embryo, for exampling by sampling in a non-destructive process a discrete number of blastomeres from a blastula

16 environmental monitoring

the practice of systematic sampling of the environment surrounding a cell or tissue production process for detection and documentation of any microbial contamination

17 exosome

a non-replicating extra-cellular vesicle secreted by living cells and that contains various constituents of its cell of origin

18 fed-batch culture

culture method used to grow cells where an addition of concentrated nutrients, or "feed," is performed for an ongoing cell/tissue culture to replenish critical nutrient levels and maximize expansion of culture in a bioprocess run

Note: fed-batch culturing techniques are critical for obtaining high cell densities, within economical constraints, typically in bioreactor systems

19 genomic modification

stable, intentional and directed change of a cell's DNA sequence using biotechnology methods

20 haplotype

a group of genes or alleles usually inherited together from a single parent, reflecting the haploid genotype

21 HLA Haplobank

a panel or repository of iPSC lines that are homozygous for HLA types and could be used to derive immunologically-compatible tissues for therapeutic transplantation

22 hyperoxia/hyperoxic

for *in vitro* cell, tissue, and organ culture, an oxygenation state higher than physioxia, such as in atmospheric or room air

22 hypoxia/ hypoxic

1. in medical terminology, a pathologic state of insufficient oxygen in the tissues
2. for *in vitro* cell and tissue culture, a pathologic state in which cells or tissues are at a partial pressure of oxygen lower than the normal physioxic state

Note: this term has been used to indicate any oxygen level lower than room air, conflating definitions for normal physiologic and abnormal pathophysiologic in vivo oxygen states. This has been confusingly paired with the terms "normoxia" or "normoxic", meaning room air oxygen levels. Because normal tissue oxygen levels are far lower than room air, in live cell, tissue, and organ culture, there is nothing physiologically normal about room air

23 investigational new drug application (IND)

a key step in development of a new drug or medical treatment in which the US Food and Drug Administration (FDA) is notified that a novel therapeutic will be used experimentally

24 ISO

The International Organization for Standardization, a centralized source of international standards for ensuring high quality products and operations across multiple industries. Publisher of the ISO quality standards for tissue-engineered medical devices

25 media exchange

a cell culture bioprocess method that involves the removal of spent media and addition of fresh media during culture to supply fresh nutrients and for removal of cellular waste products

Note 1: media exchanges should be documented to help determine media productivity and perform cost analyses on bioprocess economics

Note 2: traditional cell culture processes which require multiple full media exchanges during the culture are typically optimized for clinical processes, where reduction in the number of media exchanges or substitution with more economical fed-batch methods are implemented

26 millions of cells per liter (MCells/l)

a media productivity metric that outlines the technological and economic aspects of a bioprocess run with respect to the cell yield achieved per volume of media consumed

27 mitochondria

subcellular organelles that generate chemical energy to power cellular processes and also serve as sites for numerous metabolic processes and reactions

28 mitochondrial replacement

a potential therapy to prevent certain mitochondrial diseases by replacing mutant maternal mitochondria in an oocyte (egg) with those from an unaffected individual prior to *in vitro* fertilization

29 neural stem cells

adult stem cells that give rise to a variety of neural cells including neurons, astrocytes, and oligodendrocytes

30 niche (stem cell niche)

the micro-environment where cells reside and with which cells interact thereby impacting cell fate and physiology

31 organ engineering

the generation of a synthetic functional organ achieved by the cellularisation and vascularisation of a synthetic scaffold, or of a decellularised organ of cadaveric origin. The synthetic functional organ thus generated needs to recapitulate the function but not necessarily the shape of the natural organ

32 organ-on-a-chip

a single device with individual chambers connected by microfluidic channels for enclosing, contacting, and culturing multiple types of cells, tissues or mini-organs

33 paracrine

influence or signaling by a cell on nearby cells or tissues through localized secretion and diffusion of small molecules or proteins

34 physioxia/physioxic

the state of being at a tissue-specific physiologically normal partial pressure of oxygen

Note 1: oxygen levels *in vivo* are considerably lower than room air and vary across different ranges depending upon the local tissue type, physiology and oxygen consumption rates

Note 2: this has been called "physiologic normoxia" in the past

35 platelet-rich plasma

a blood plasma enriched in platelets and which contains a cocktail of cytokines and growth factors in higher concentrations that in blood plasma

36 RNA-Seq

an analytical method that can reveal the identities and quantities of RNAs expressed from genes in a cellular sample

37 stem cell tourism

seeking or receiving stem-cell based treatments for disease or injury from clinics or practitioners that offer untested or unproven therapies

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The New York Stem Cell Foundation (NYSCF) combines the depth of a highly focused research institute with the breadth of a wide-ranging philanthropic organization. Since its establishment in 2005, NYSCF has invested over $160 million in stem cell research and continues to conduct the most advanced stem cell research internationally, both in its own Research Institute in New York City, and also in collaboration with major medical research and leading academic institutions around the world.

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NxR Biotechnologies is a consulting firm assisting life science companies and academic institutions conduct business development or investment initiatives. Particularly, NxR provides services for performing strategic, scientific, and commercial assessments; writing business plans; gathering competitive intelligence; and implementing partnership or in/out-licensing of conventional or regenerative medicine products, and commercialization deals. Areas of focus encompass the pharmaceutical industry and the white biotechnology industry. In the pharmaceutical industry, NxR focuses on cell-based and gene-based therapeutics, nucleic acid therapeutics, and biologics. In the white biotechnology industry, areas of specialization comprise sustainable chemicals including biomass conversion, biofuels, and polymers, as well as high value-added fermentation products including amino acids, proteins, and pharmaceuticals.

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BSI FOREWORD

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This PAS is not to be regarded as a British Standard. It will be withdrawn upon publication of its content in, or as, a British Standard.

The PAS process enables a specification to be rapidly developed in order to fulfil an immediate need in industry. A PAS may be considered for further development as a British Standard, or constitute part of the UK input into the development of a European or International Standard.

Supersession

This PAS supersedes PAS 84:2008, which is withdrawn.

Information about this document

This is a full revision of the PAS and introduces the following principal changes:

- Update of existing terms and definitions for accuracy and relevance
- Addition of new terms that have appeared within the research, clinical, bioprocessing and regulatory space since the last revision
- Update of the annex on regulatory terms to reflect changes in legislation and include regulatory terms used in the USA as well as in the UK and Europe
- Addition of an annex on finance terms that are likely to be of use to the cell therapy and regenerative medicine community

Relationship with other publications

This PAS provides a set of terms and definitions that is of relevance to the cell therapy and regenerative medicine industry.

It includes definitions of terms used in:

- PAS 83, Developing human cells for clinical applications in the European Union and the United States of America – Guide
- PAS 93, Characterization of human cells for clinical applications – Guide

Where possible, an attempt has been made to use terms and definitions that have been defined in existing standards, in particular ASTM F2312-11, Standard terminology relating to tissue engineered medical products.

A number of regulations exist that are relevant to the field of cell therapy and regenerative medicine. These regulations contain terms that are defined in some detail. In some instances regulatory definitions have been included verbatim. However, in order for this PAS to achieve its intended objective, more succinct and precise definitions consistent with regulations have been developed.

Presentational conventions

The terms and definition in the PAS are presented in roman (i.e. upright) type.

Commentary, explanation and general informative material is presented in smaller italic type.

When terms defined in this PAS are used in the definition or notes of another term, they are shown in bold type.

Where a term has been given a meaning narrower than its generally accepted meaning, a qualification has been included in angular brackets at the start of the definition denoting the context within which it has been defined, i.e. <…>.

Spelling conforms to The Shorter Oxford English Dictionary. If a word has more than one spelling, the first spelling in the dictionary is used.

Feedback

Feedback on the technical content of this PAS can be submitted through the BSI Document Feedback system
http://feedback.bsigroup.com.

Any feedback received will be reviewed when developing future revisions of this document.

Contractual & legal considerations

Attention is drawn to the following statutory regulations.

- European Directive 2001/83/EC relating to medicinal products for human use (and amendments) [1]
- European Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells [2] implemented in the UK by Human Tissue (Quality and Safety for Human Application) Regulations 2007 [3]
- European Directive 2010/45/EU on standards of quality and safety of human organs intended for transplantation [4]
- European Regulation No. 1394/2007 on advanced therapy medicinal products [5]
- Human Fertilisation and Embryology Act 1990 (and amendments) [6]
- Human Tissue Act 2004 [7]
- Human Tissue (Scotland) Act 2006 (and amendments) [8]

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

Compliance with a PAS cannot confer immunity from legal obligations.

INTRODUCTION

This PAS has been developed to encourage the use of common terms and definitions within the field of cell therapies and regenerative medicine. For the purpose of this PAS:

- Cell therapy is a "therapy in which cells are administered to the body to the benefit of the recipient"; and
- Regenerative medicine is a "process for replacing or regenerating cells, tissues or organs, to restore or establish normal function".

There has been increasing scrutiny of current standardization and regulations by researchers, manufacturers and the general public as cell therapy products and regenerative medicine products move nearer to commercialization.

UK stakeholders identified a need for standardization to achieve consensus on the terms and definitions used within cell therapies and regenerative medicine. Using the views and opinions of key UK stakeholders, this PAS has been developed to meet this need. The first edition of PAS 84 was published in 2008 and since then a number of developments have taken place in this field. As such, this revision of PAS 84 has been conducted to introduce changes that reflect these developments.

The aim of this PAS is to provide clear guidance on the meaning of terminology currently used within this field in the UK by industry, regulators, government and academia. Where applicable, terms and definitions have been aligned with existing regulations, codes of practice or standards. The sources of reproduced or adapted terms and definitions are referenced within this PAS.

It is recognized that there are international differences in terminology in current use, such as between the USA and Europe and particularly with regard to regional legislation. In this case, the European legislative or common terms have been used where possible.

It is intended that this document will help UK stakeholders to:

- Prepare for legal, commercial and societal issues;
- Facilitate a common understanding of the science of cell therapies and regenerative medicine;
- Improve communication and understanding of advances in the field;
- Demonstrate best practice and product quality; and
- Reduce research, development, production and transaction costs.

1. SCOPE

This PAS lists terms and definitions:

- Associated with the naming of types of cell therapy and regenerative medicine products; and
- That describe materials, processes, methodologies and applications within cell therapies and regenerative medicine.

It covers:

- General terms;
- Cell and tissue components;
- Non-cellular components;
- Cell and tissue procurement;
- Measurement and analysis;
- Manufacturing and production; and
- Clinical trials.

Alternative definitions of terms found in regulations relevant to the cell therapy and regenerative medicine industry are covered in **Annex A**.

Finance terms and definitions relevant to the cell therapy and regenerative medicine industry are covered in **Annex B**.

2. TERMS & DEFINITIONS

2.1 acceptance criteria

predetermined criteria for acceptance of a test result

NOTE Such criteria can include numerical limits and ranges.

[derived from the European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, Part II [9]]

2.2 active implantable medical device

active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure

[European Directive 90/385/EEC (and amendments) [10]]

2.3 active medical device

medical device relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity

[European Directive 90/385/EEC (and amendments) [10]]

2.4 active substance

substance or mixture of substances intended to be used in the **manufacture** of a **medicinal product** and that, when used in the production of a medicinal product, becomes a part of the medicinal product that furnishes pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or affects the structure and function of the body

NOTE 1 Also known as active pharmaceutical ingredient (API) and drug substance.
NOTE 2 See also **cellular active substance**.

[derived from ICH Harmonised Tripartite Guideline Q7 [11]]

2.5 active surveillance

surveillance ascertaining the number of **adverse events** via a continuous pre-organized process

NOTE Examples include the follow-up of patients treated with a particular **medicinal product** through a **risk management** programme. In general, it is more feasible to obtain comprehensive data on individual adverse events through active surveillance than through **passive surveillance**.

[derived from the European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 9A [12]]

2.6 admixed embryo

embryo that contains both human and animal material

NOTE 1 Also known as **hybrid embryo**.

NOTE 2 Examples include an **animal chimera embryo**, a **cytoplasmic hybrid embryo (cybrid)** a **human chimera embryo** and a **transgenic human embryo**.

NOTE 3 A legal definition of human admixed embryo applicable in the UK is given in Table A.1.

NOTE 4 See also **permitted embryo**.

2.7 adult stem cell

stem cell derived from an adult body or fetus

NOTE Also known as somatic stem cell or stromal stem cell.

[derived from the UK Stem Cell Bank's Code of Practice for the Use of Human Stem Cell Lines [13]]

2.8 advanced therapy medicinal product

medicinal product for human use that is a gene therapy medicinal product, a somatic cell therapy medicinal product or tissue engineered product

[European Regulation No. 1394/2007 [5]]

2.9 adventitious

coming from an external source

2.10 adventitious agent

unintentionally introduced infectious **contaminant**

[derived from ASTM F2312-11]

2.11 adverse event

unexpected occurrence that might have an influence on a patient or **clinical trial subject** who has been administered a **medicinal product**, and that is not necessarily caused by the product

NOTE 1 A legal definition applicable in the EU for clinical trials is given in Table A.1.

NOTE 2 Also known as adverse experience. A legal definition of adverse experience applicable in the USA is given in Table A.1.

NOTE 3 See also **serious adverse event (SAE)**.

2.12 adverse event reporting

system for notification to an authority of **adverse events**

NOTE Notification can be made to national regulatory authorities as well as international authorities such as the World Health Organization (WHO).

2.13 adverse reaction

response to a **medicinal product** which is noxious and unintended

NOTE 1 Two legal definitions applicable in the EU are given in Table A.1, the first relating to clinical trials and the second relating to medicinal products for human use.

NOTE 2 See also **serious adverse reaction (SAR)** and **unexpected adverse reaction (UAR)**.

2.14 allogeneic

where **donor** and recipient are different individuals

2.15 allograft

allogeneic graft

NOTE Also known as homograft.

2.16 ancillary material

components used during the **manufacture** of a **medicinal product** that are not deliberately present in the medicinal product

NOTE Examples include **cytokines**, **growth factors**, monoclonal antibodies, cell-separation devices and media components.

2.17 animal chimera embryo

admixed embryo created by inserting human cells into an animal embryo

[derived from the Human Fertilisation and Embryology Authority's report on hybrids and chimeras [**14**]]

2.18 apoptosis

programmed cell death

NOTE See also **necrosis**.

2.19 arm

treatment or patient group in a **randomized trial**

2.20 aseptic technique

manner of handling or processing where the risk of **contamination** with living or dead bacteria, fungi or viruses and other **biological agents** is minimized or prevented

2.21 asymmetric cell division

cell division where each daughter cell has a different cellular fate

2.22 audit

documented, systematic evaluation to determine whether approved policies, **standard operating procedures** or operations have been properly implemented and are being followed

[NetCord-FACT's International Standards for Cord Blood collection, Processing, and Release for Administration **[15]**]

2.23 autograft

autologous graft

2.24 autologous

where **donor** and recipient are the same individual

2.25 baseline

information gathered at the beginning of a study from which variations found in the study are measured

2.26 batch (or lot)

defined quantity of **starting material**, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous

NOTE To complete certain **manufacturing** steps, it may be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch corresponds to a defined fraction of the production, characterized by its intended homogeneity.

[derived from the European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, Glossary **[16]**]

2.27 batch (or lot) number

unique combination of numbers, letters and/or symbols that identifies a **batch (or lot)** and from which the production and distribution history can be determined

[European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, Glossary **[16]**]

2.28 bioactive agent

agent that has a biological effect on cells or **tissue**

2.29 bioaesthetics

regenerative medicine-like therapies aimed at **cosmesis** rather than traditional medical alignments

2.30 bioburden

quantity and type of microorganisms present in a **raw material**, **intermediate** or **active substance**

NOTE Bioburden is considered **contamination** when the quantity of microorganisms has exceeded an accepted level or the microorganisms detected are of an objectionable type.

[derived from the European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, Part II [9]]

2.31 biocompatibility

ability of a material to perform with an appropriate host response in a specific application

[The Williams Dictionary of Biomaterials [17]]

2.32 biodistribution

dispersal of **biological agents** or **medicinal products** throughout a human or animal body

2.33 biological agent

microorganism, **cell culture** or human endoparasite, whether or not genetically modified, which can cause infection, allergy, toxicity or otherwise create a hazard to human health

[The Control of Substances Hazardous to Health Regulations 2002 [18]]

2.34 biological medicinal product

product, the **active substance** of which is **a biological substance**

NOTE Also known as biologic.

[European Directive 2001/83/EC (and amendments) [1]]

2.35 biological substance

substance that is produced by or extracted from a biological source and that needs, for its characterization and the determination of its **quality**, a combination of physicochemical–biological testing together with the production process and its control

[European Directive 2001/83/EC (and amendments) [1]]

2.36 biomarker

molecular indicator of a specific biological property

2.37 biomaterial

material intended to interface with biological systems to evaluate, treat, augment or replace any **tissue**, **organ** or function of the body

[BS EN ISO 10993-6:2009, 3.3]

2.38 biomolecule

biologically active peptide, protein, carbohydrate, vitamin, lipid or nucleic acid produced by and purified from naturally occurring or recombinant organisms, **tissues** or **cell lines** or synthetic analogs of such molecules

[ASTM F2312-11]

2.39 bioprocessing

activity performed on cells, **tissues** and **organs** other than collection

NOTE For example, preparation and **preservation** for storage and packaging.

2.40 bioreactor

device, equipment or apparatus designed to contain structures, both cellular and molecular, that are capable of taking part in a specific biological process and from which the products of the process can be harvested or extracted

[The Williams Dictionary of Biomaterials [17]]

2.41 biosimilar

new **biological medicinal product** claimed to be similar in terms of quality, safety and efficacy to a reference **medicinal product** that has been granted a **marketing authorization** in the community

NOTE Also known as similar biological medicinal product.

[derived from the definition of similar biological medicinal product in the European Medicines Agency's Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues [19]]

2.42 blastocyst

pre-implantation embryo of about 150 cells produced by **cell division** around 144 hours following fertilization

NOTE 1 The blastocyst is a sphere made up of an outer layer of cells (the **trophoblast**) and the **inner cell mass**.

NOTE 2 See also **morula**.

[derived from the Stem Cell Information Glossary [20]]

2.43 blastomere

cell contained within a **morula**

2.44 cancer vaccine

therapy intended to stimulate a primary immune response to **tumour-associated antigens**, with the intention of inducing **tumour** regression

NOTE Also known as cancer immunotherapy.

2.45 cell authenticity

degree to which a population of cells has the correct identity and is free of other cell types

NOTE The **quality** of the authentication depends on the specificity and sensitivity of the technique used.

2.46 cell bank

collection of cells of uniform composition stored under defined conditions

NOTE 1 Uniform composition refers to the collection of cells being representative of the original cell culture or cultures from which they are derived.

NOTE 2 A two-tiered cell banking system consisting of a **master cell bank (MCB)** and **working cell bank (WCB)** is commonly used for **cell lines** that are to be used extensively within a process.

[derived from ICH Harmonised Tripartite Guideline Q5D [21]]

2.47 cell-based medicinal product (CBMP)

medicinal product containing cells

NOTE These products may be combined with non-cellular components and may include genetically modified human cells.

[derived from the European Medicines Agency's Guideline on Human Cell-Based Medicinal Products [22]]

2.48 cell culture

in vitro growth and maintenance of cells

2.49 cell division

process by which a cell divides to form daughter cells

NOTE See also **asymmetric cell division**.

2.50 cell expansion

increase in the number of cells by their **proliferation**

2.51 cell line

characterized **cell culture** that has been demonstrated to be phenotypically and genotypically consistent over a specified number of **population doublings**

2.52 cell migration

movement of cells in response to a stimulus

2.53 cell morphology

microscopic study of the form and structure of cells

2.54 cell selection

separation of a homogenous population of cells from a heterogeneous population

2.55 cell surface marker

biomolecule expressed on the surface of a cell and is used to identify cell type

2.56 cell therapy

therapy in which cells are administered to the body to the benefit of the recipient

2.57 cell therapy product

product consisting of cells used for **cell therapy**

2.58 cell viability

measure of a cell's potential for metabolism or multiplication

2.59 cellular active substance

active substance that consists of cells and/or **tissue**

2.60 cellular starting material

starting material that consists of cells and/or **tissue**

2.61 centralized authorization procedure

procedure leading to a **marketing authorization**

NOTE 1 This procedure is administered by the European Medicines Agency (EMA) in accordance with European Regulation No. 726/2004 [23]. The procedure is mandatory for certain **medicinal products**, including all advanced therapy medicinal products (ATMPs).

NOTE 2 Also known as centralized procedure.

2.62 chief investigator

investigator who takes overall charge of a multi-centre study

NOTE See also **clinical investigator** and **principal investigator**.

2.63 chimera

organism consisting of two or more **tissues** of different genetic composition

NOTE Conventionally produced by the injection of **embryonic stem cells** into a recipient **blastocyst** or in adults following **haematopoietic stem cell transplantation**.

2.64 chimerism

condition of being a **chimera**

2.65 cleanroom (or clean facility)

room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary

[BS EN ISO 14644-1:1999, 2.1.1]

2.66 clinical equivalent

medicinal product that contains essentially an identical amount of an identical **active substance** to that found in another medicinal product, and that provides an identical therapeutic effect to that other medicinal product

NOTE 1 A decision on whether a therapeutic effect is considered identical to another therapeutic effect is determined by assessing the extent to which a symptom or disease is controlled by the medicinal product.

NOTE 2 Also known as therapeutic equivalent.

2.67 clinical follow-up

follow-up of patients conducted by a healthcare professional

NOTE 1 It includes prevention, screening, monitoring, diagnosis and treatment of diseases, injuries, complications, **adverse reactions** and medical errors.

NOTE 2 See also **post-market surveillance**.

[European Medicines Agency's Guideline on safety and efficacy follow-up – Risk management of advanced therapy medicinal products **[24]**]

2.68 clinical hold

delay of a proposed **clinical trial** or suspension of an ongoing **clinical trial**

NOTE Attention is drawn to the US Code of Federal Regulations, 21CFR312.42(a) **[25]**, which legislated for the use of clinical hold orders by the US Food and Drug Administration (FDA).

2.69 clinical investigator

medical researcher who is responsible for a **clinical trial's protocol**

NOTE See also **chief investigator** and **principal investigator**.

2.70 clinical research organization (CRO)

organization that assumes, as an independent contractor with the sponsor of a **clinical trial**, one or more of the obligations of the sponsor with respect to the **clinical trial**

NOTE 1 These obligations might include design of a **protocol**, selection or monitoring of investigations, evaluation of reports and preparation of materials to be submitted to a relevant authority.

NOTE 2 See also **contract manufacturing organization (CMO)** and **contract research organization (contract RO)**.

2.71 clinical translation

process of taking a treatment from the laboratory to testing in volunteers

2.72 clinical trial

investigation in human **subjects** intended to discover or verify the **safety** and efficacy of a **therapy**

NOTE Legal definitions applicable in the EU and USA are given in Table A.1.

2.73 clone

genetically identical copy of a cell or organism

2.74 cloning

isolation and production of a genetically identical copy of a cell or organism

NOTE 1 This can be conducted via **somatic cell nuclear transfer**.

NOTE 2 This is to be distinguished from molecular or gene cloning, which refers to the identification and copying of a specific gene sequence rather than a whole cell or organism.

2.75 clonogenic cell

single cell able to proliferate into a colony of genetically identical cells

2.76 closed system

system in which a **medicinal product** is not exposed to the immediate room environment during **manufacture**

[derived from the European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, draft Annex 2 [26]]

2.77 colony forming unit (CFU)

macroscopic colony formed after the introduction of one or more microorganisms to microbiological growth media

NOTE One colony forming unit is expressed as 1 CFU.

[US Food And Drug Administration's Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice [27]]

2.78 combination cell therapy

combination product containing a cell **therapy product**

NOTE See also **combination product** and **combined advanced therapy medicinal product (combined ATMP)**.

2.79 combination product

product that is a combination of a medicinal product and/or biological medicinal product and/or medical device

NOTE See also **combination cell therapy** and **combined advanced therapy medicinal product (combined ATMP)**.

2.80 combined advanced therapy medicinal product (combined ATMP)

product that incorporates one or more **medical devices** or one or more **active implantable medical device**s and either its cellular or **tissue** part contains viable cells or tissues, or its cellular or tissue part containing non-viable cells or tissues is liable to act upon the human body with action that can be considered as primary to that of the devices referred to

NOTE See also **advanced therapy medicinal product (ATMP)**, **combination cell therapy** and **combination product**.

[European Regulation No. 1394/2007 [5]]

2.81 comparability

exercise to evaluate the impact of changes to a manufacturing process on the validity of **quality**, non-clinical and/or clinical data relating to a **cell therapy product** or its components

NOTE The components of a **cell therapy product** include, for example, cellular populations and **cell banks**.

2.82 comparable

conclusion that a **medicinal product** has highly similar **quality** attributes before and after **manufacturing** process changes and that no adverse impact on the **safety** or efficacy, including **immunogenicity**, of the product occurred

NOTE This conclusion can be based on an analysis of quality attributes. In some cases, non-clinical or clinical data might contribute to the conclusion.

[derived from ICH Harmonised Tripartite Guideline Q5E [28]]

2.83 comparative genomic hybridization (CGH)

method for the analysis of copy number changes in the chromosomal DNA content of a cell or **tissue**

2.84 competent authority

person or organization that has the legally delegated or invested authority, capacity, or power to perform a designated function

NOTE This will sometimes be referred to as a national competent authority (NCA), since authorities in different countries have different responsibilities.

2.85 conditioning

<patient care> medical procedure used to prepare a patient for the application of a **medicinal product**

NOTE Examples include **therapeutic immunosuppression**, destruction of the patient's bone marrow, use of hormones for stimulation or inhibition of certain physiological functions.

[European Medicines Agency's Guideline on safety and efficacy follow-up – Risk management of advanced therapy medicinal products [24]]

2.86 confounding factor

variable that has the potential to interfere with the interpretation of data resulting from a scientific study, technical study or **clinical trial**

2.87 contained use

operation in which **genetically modified organisms** are cultured, stored, used, transported, destroyed or disposed of and for which physical, chemical and/or biological barriers are used to limit their contact with the general population and the environment

[derived from European Directive 90/219/EEC (and amendments) [29]]

2.88 contamination

undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a **raw material**, **intermediate** or **active substance** during production, sampling, packaging or repackaging, storage or transport

[derived from the European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, Part II [9]]

2.89 contaminant

impurity of a chemical or microbiological nature, or foreign matter, unintentionally introduced into or onto a **raw material**, **intermediate** or **active substance** during production, sampling, packaging or repackaging, storage or transport

[derived fromthe European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, Part II [9]]

2.90 continued process verification

assurance that during routine production a process remains in a **state of control**

[US Food And Drug Administration's Guidance for Industry – Process Validation: General Principles and Practices [30]]

2.91 continuous cell line

cell line that appears to have the capacity for indefinite **cell division**

NOTE See also **finite cell line**.

2.92 contract manufacturing organization (CMO)

organization performing some aspect of **manufacturing** on behalf of another party

NOTE See also **clinical research organization (CRO)** and **contract research organization (contract RO)**.

2.93 contract research organization (contract RO)

organization that assumes, as an independent contractor with the sponsor of any type of research, one or more of the obligations of the sponsor

NOTE 1 These obligations might include design of a **protocol**, selection or monitoring of investigations, evaluation of reports and preparation of materials to be submitted to a relevant authority.

NOTE 2 See also **contract manufacturing organization (CMO)** and **clinical research organization (CRO)**.

2.94 control

benchmark against which experimental observations are evaluated

2.95 controlled trial

comparative **clinical trial** involving a **control**

2.96 cord blood

blood isolated from an umbilical cord at birth

2.97 cord blood stem cell

stem cell isolated from **cord blood**

2.98 cord blood transplantation

transfusion of **cord blood**

2.99 cosmesis

preservation, restoration or bestowing of bodily beauty

[Dorland's Medical Dictionary [31]]

2.100 cost benefit analysis

form of economic evaluation which attempts to value the consequences of a **therapy** in monetary terms in order to ascertain whether the beneficial consequences of the programme justify the costs

[derived from Methods for the Economic Evaluation of Health Care Programmes [32]]

2.101 cross-contamination

unintended presence of a cell or a material with another cell or material

NOTE This can occur during a cell **manufacturing** process as a result of the inadvertent switching or mixing of **cell cultures**.

[derived from ASTM F2312-11]

2.102 cryopreservation

maintenance of the viability of cells, **tissues** and **organs** by the process of **cryoprotection**, cooling and storing at very low temperatures

NOTE See also **vitrification**.

2.103 cryoprotectant

agent used to protect cells, **tissues** and **organs** from damage that can occur during cooling and storing at very low temperatures

NOTE 1 An example of damage is intracellular ice crystal formation.

NOTE 2 See also **cryoprotection**.

2.104 cryoprotection

protection of cells, **tissues** and **organs** from damage that can occur during cooling and storing at very low temperatures

NOTE See also **cryoprotectant**.

2.105 culture medium

nutrient supply used to support the growth and expansion of cells or to maintain **tissue** or **organ** cultures

2.106 cytokine

intercellular signalling **biomolecule**

2.107 cytoplasmic hybrid embryos (cybrid)

admixed embryo created by replacing the nucleus of an animal egg or a cell derived from an animal embryo with a human cell or the nucleus of a human cell

[derived from the Human Fertilisation and Embryology Authority's report on hybrids and chimeras [**14**]]

2.108 de-differentiation

regression of a cell to a less specialized **phenotype**

2.109 differentiation

development into a more specialized cell **phenotype**

2.110 defined medium

culture medium in which all components are known

2.111 direct use

donation and use of cells that does not involve storage in a **cell bank**

[derived from European Directive 2006/17/EC [33]]

2.112 DNA profiling

technique to identify an organism from its DNA

NOTE Also known as DNA fingerprinting.

2.113 DNA short tandem repeat profiling (DNA STR profiling)

DNA profiling by recognizing short sequence elements present throughout a DNA molecule

2.114 donation

process of providing human **tissues** or cells with **informed consent**

NOTE This does not include the donation of **organs** for **transplantation** as this is not part of regenerative medicine.

2.115 donor

source from which cells or **tissues** are derived for **cell therapy** and **regenerative medicine**

[derived from European Directive 2004/23/EC [2]]

2.116 donor selection

process of selecting **donors** against **eligibility criteria**

2.117 dose

prescribed quantity of a medicine or of a remedial agent

[Larousse Dictionary of Science and Technology [34]]

2.118 dose finding study

study in which different groups of patients are given different **doses** of a product to select the best doses for use in later, larger-scale trials

2.119 double-blind trial

randomized trial in which the clinician and patient are unaware of which **arm** of the trial the patient is on

NOTE 1 See also **single-blind trial**.

NOTE 2 Contrasts with **open-label trial**.

2.120 downstream processing

technologies involved in the recovery and purification of products

NOTE Contrast with **upstream processing**.

2.121 efficacy follow-up

systematic collection and collation of data that is designed in a way that enables learning about the efficacy or effectiveness of a **medicinal product**

NOTE It can include **active surveillance**, **clinical trials**, **observational trials** and **passive surveillance**.

[European Medicines Agency's Guideline on safety and efficacy follow-up – Risk management of advanced therapy medicinal products [24]]

2.122 eligibility criteria

predetermined criteria for establishing whether an individual may or may not be entitled to be chosen

NOTE Also known as inclusion and exclusion criteria.

2.123 embryonic stem cell

undifferentiated cell derived from a pre-blastocyst or **blastocyst** that is **pluripotent**

2.124 embryonic stem cell line

cell line consisting of **embryonic stem cells**

2.125 encapsulation

procedure by which biological materials are enclosed within a microscopic or macroscopic semipermeable barrier

[derived from ASTM F2312-11]

2.126 endpoint

overall outcome that a **protocol** is designed to evaluate

2.127 engineered cells &/or tissues

cells or **tissues** that have been subjected to **substantial manipulation**, so that the biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved; and that are not intended to be used for the same essential function or functions in the recipient as in the **donor**

NOTE The manipulations listed in Annex I to European Regulation No. 1394/2007 [5], in particular, are not considered as substantial manipulations.

[European Regulation No. 1394/2007 [5]]

2.128 engraftment

process of integration of cellular material into a recipient

2.129 epigenetic

heritable change in the heritable pattern of gene expression that is mediated by mechanisms other than alterations in the primary nucleotide sequence of a gene

NOTE For example, DNA methylation or histone modifications.

[derived from Epigenetic mechanisms of gene regulation [35]]

2.130 ethics committee

independent body consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, **safety** and well-being of human **subjects** involved in a study

NOTE 1 Legal definitions applicable in the EU and USA are given in Table A.1.

NOTE 2 A hierarchy of ethical committees exists. The committees are known as the local research ethics committee (LREC), the multi-centre research ethics committee (MREC) and the central office for research ethics committee (COREC).

2.131 *ex vivo*

outside the living body

2.132 excipient

ingredient added intentionally to an **active substance**, which does not have pharmacological properties in the quantity used

[derived from ICH Harmonised Tripartite Guideline Q1A(R2) [36]]

2.133 extracellular matrix (ECM)

non-cellular matrix surrounding cells

2.134 extracorporeal

situated or occurring outside the body

2.135 false negative

<statistics> erroneously recognized as bad or false

NOTE Contrasts with **false positive**.

2.136 false positive

<statistics> erroneously recognized as good or true

NOTE Can be due to a failure in an alerting system or due to an error made in a statistical decision process.

2.137 feeder cell

cell used in co-culture to sustain the viability and desired characteristics of other cells

2.138 fetal stem cell

multipotent stem cell originating from a fetus that has the potential to differentiate into or generate a limited range of specialized cell types

2.139 finite cell line

cell line that can be maintained for a limited number of **population doublings** before it becomes senescent and ultimately loses the ability to divide

NOTE See also **continuous cell line**.

2.140 flow cytometry

technique that measures and analyses light scatter and fluorescence from single cells as they flow in a fluid stream through a laser beam

NOTE This can be used to determine the **phenotype** of single cells.

2.141 fluorescence activated cell sorting (FACS)

sorting of a heterogeneous mixture of cells into two or more containers, one cell at a time, using the specific light scattering and fluorescent characteristics of each cell

NOTE See also **magnetic-based cell sorting**.

[derived from The Williams Dictionary of Biomaterials [17]]

2.142 gene expression profile (transcriptome)

spectrum of mRNA levels resulting from gene activity at a given time

2.143 gene therapy

deliberate manipulation of genetic material into cells for therapeutic purpose

NOTE See also **gene therapy medicinal product**.

2.144 gene therapy medicinal product

biological medicinal product which contains an **active substance** which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; and whose therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence

NOTE 1 This does not include vaccines against infectious diseases.

NOTE 2 See also **gene therapy**.

[European Directive 2001/83/EC (and amendments) [1]]

2.145 gene transfer

process of transferring a gene into cells, involving an expression system contained in a delivery system known as a **vector**, which can be of viral as well as non-viral origin

NOTE After gene transfer, genetically modified cells are also termed transduced cells.

[European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, draft Annex 2 **[26]**]

2.146 genetic locus

specific location of a gene or DNA sequence on a chromosome

2.147 genetically modified organism (GMO)

organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination

[derived from European Directive No. 2001/18/EC (and amendments) **[37]**]

2.148 genotype

genetic constitution of an individual cell or organism

2.149 Good Cell Culture Practice (GCCP)

guidelines to define minimum standards in cell and **tissue** culture

NOTE Also known as current Good Cell Culture Practice (cGCCP).

2.150 Good Clinical Practice (GCP)

regulations, codes and guidelines covering the conduct of **clinical trials**

NOTE Also known as current Good Clinical Practice (cGCP).

2.151 Good Laboratory Practice (GLP)

regulations, codes and guidelines for laboratories conducting **non-clinical studies**

NOTE Also known as current Good Laboratory Practice (cGLP).

2.152 Good Manufacturing Practice (GMP)

regulations, codes and guidelines for the **manufacture** of **cell therapy products**, **medicinal products**, **medical devices**, diagnostic products, food products and **active substances**

NOTE Also known as current Good Manufacturing Practice (cGMP).

2.153 Good Tissue Practice (GTP)

regulations, codes and guidelines for the **manufacture** of **cell therapy products**

NOTE Also known as current Good Tissue Practice (cGTP).

2.154 graft versus host disease (GVHD)

aggressive immune response caused when T-cells derived from **donor** cells recognize the **tissue** of a recipient

NOTE This can occur following a **stem cell** or bone marrow **transplantation**.

2.155 growth factor

naturally occurring protein capable of stimulating cellular **proliferation** and/or **differentiation**

2.156 haemocytometer

glass slide with a chamber for counting cells in a given volume

2.157 haematopoiesis

formation of blood lineages from **haematopoietic stem cells**

2.158 haematopoietic stem cell (HSC)

stem cell that gives rise to all red and white blood cells and platelets

[derived from the Stem Cell Information Glossary [20]]

2.159 Hayflick limit

number of divisions a cell can undergo before it stops dividing further

2.160 heterologous use

different use

2.161 heterotopic

different anatomical location

2.162 histocompatibility

measure of the extent to which implanted cells are immunologically matched to the recipient

2.163 histology

microscopic study of the form and structure of **tissues**

2.164 homologous use

same essential function

2.165 homotopic

same anatomical location

NOTE Also known as orthotopic.

2.166 human chimera embryo

admixed embryo created by inserting animal cells into a human embryo

[derived from the Human Fertilisation and Embryology Authority's report on hybrids and chimeras [14]]

2.167 human leucocyte-associated antigen (HLA)

highly polymorphic molecule required for antigen presentation encoded within the human **major histocompatibility complex**

NOTE See also **tissue typing**.

2.168 immobilization

entrapment of materials within, or bound to, a matrix

[derived from ASTM F2312-11]

2.169 immortal

capacity of cells to proliferate indefinitely

2.170 immunocytochemistry

method that uses antibodies to identify, locate and visualize specific molecules in or on the surface of cells

2.171 immunogenicity

extent to which an administered substance provokes an immune response in the recipient

2.172 immunohistochemistry

method that uses antibodies to identify, locate and visualize specific molecules or cell types in **tissue** sections

2.173 immunological rejection

failure of a recipient's body to accept a transplanted **tissue** or **organ** as the result of immunological incompatibility

2.174 immunomodulation

therapeutic strategy aimed at altering the normal course of an immune response, either enhancing it for the purpose of vaccination or suppressing its effects if deleterious

NOTE This is often used in the case of **allograft** rejection and autoimmunity.

2.175 immunotherapy

planned intervention in the normal course of a potentially detrimental immune response, intended to solicit an outcome of benefit to an individual

2.176 impurity

component present in a substance that is not the desired substance

2.177 *in vitro*

within an artificial environment

2.178 *in vivo*

within the living body

2.179 in-process control

checks performed during processing in order to monitor and if necessary adjust the process to ensure that the product conforms to its **specification**

NOTE 1 Environmental conditions and equipment can, for example, be monitored as part of in-process control.

NOTE 2 One element of in-process control is **process analytical technology (PAT)**.

2.180 induced pluripotent stem cell (iPS cell)

human **embryonic stem cell**-like cell that is produced by **reprogramming** a cell to a state of pluripotency

2.181 informed consent

voluntary decision to take part in a **clinical trial** or donate cells or tissues, after being duly informed of the nature, significance, implications and risks associated with the clinical trial or **donation**, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative

NOTE 1 Legal definitions applicable in the EU and USA for clinical trials are given in Table A.1.

NOTE 2 The annex to European Directive 2004/23/EC [2] specifies the information that must be provided to a donor, their relatives or any person granting authorization on behalf of a donor.

NOTE 3 In the UK, detailed advice on when and how consent should be sought, and what information should be given is provided in the Human Tissue Authority Code of practice 1 [38].

2.182 inner cell mass (ICM)

cluster of cells inside a **blastocyst**

NOTE These cells are used to generate **embryonic stem cells**.

[derived from the Stem Cell Information Glossary [20]]

2.183 intermediate

material produced during steps in the processing of an **active substance** that undergoes further molecular change or purification before it becomes an **active substance**

NOTE Intermediates may or may not be isolated.

[derived from the European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, Part II [9]]

2.184 investigational medicinal product (IMP)

pharmaceutical form of an **active substance** or **placebo** being tested or used as a reference in a **clinical trial**

NOTE 1 This includes products already with a **marketing authorization** but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

NOTE 2 Also known in the USA as investigational new drug (IND).

[derived from European Directive 2001/20/EC [39]]

2.185 karyotyping

assessment of the complete set of all chromosomes of a cell that can identify chromosomal abnormalities

2.186 magnetic-based cell sorting

sorting of a heterogeneous mixture of cells via mixing with magnetic beads coated with antibodies against specific cell surface antigens, followed by separation and selection using a column placed in a magnetic field

NOTE See also **fluorescence activated cell sorting (FACS)**.

2.187 major histocompatibility complex (MHC)

genetic locus encompassing a family of highly polymorphic genes encoding proteins that regulate immune responses

NOTE The **human leucocyte-associated antigen (HLA)** is encoded within the human MHC.

2.188 manufacture

any or all of the steps in the recovery, screening, testing, processing, storage, labelling or packaging of any **cell therapy product**

[derived from ASTM F2312-11]

2.189 marketing authorization

authorization by a relevant authority for a **medicinal product** to be placed on the market

NOTE 1 A new drug application (NDA) is the vehicle by which drug sponsors formally propose that the US Food and Drug Administration approve a new pharmaceutical for sale and marketing in the USA.

NOTE 2 A biologics licence application (BLA) is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce in the USA.

2.190 marrow stromal cell

differentiated progeny from **mesenchymal stem cells**

NOTE Typically a heterogeneous population including a range of **stromal cells** at different stages of **differentiation** and of different composition or nature including osteoblasts (bone), chondrocytes (cartilage) and adipocytes (fat).

2.191 master cell bank (MCB)

cell bank prepared from an aliquot of a single pool of cells

NOTE 1 Generally the pool of cells is prepared from a **clone** under defined conditions.

NOTE 2 In a two-tiered cell banking system, the MCB is used to derive the **working cell bank (WCB)**.

[derived from ICH Harmonised Tripartite Guideline Q5D [21]]

2.192 medical device

instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease; diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or of a physiological process; control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

[European Directive 93/42/EEC (and amendments) **[40]**]

2.193 medicinal product

substance or combination of substances presented as having properties for treating or preventing disease in human beings; or 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

[European Directive 2001/83/EC (and amendments) **[1]**]

2.194 mesenchymal stem cell

multipotent bone marrow-derived non-**haematopoietic stem cell** with the capacity to generate cells of the stromal lineage

NOTE 1 Examples of cell types that can be derived from mesenchymal stem cells include osteoblasts, chondrocytes and adipocytes.

NOTE 2 These cells are also referred to as mesenchymal stromal stem cells.

2.195 microarray

set of DNA or protein molecules spotted onto a solid matrix for use in multiplex probing of a biological sample to determine gene or **protein expression**, marker pattern or the nucleotide sequence of DNA/RNA

2.196 minimal manipulation

processing that does not alter the relevant biological characteristics of cells or **tissue**

NOTE Contrasts with **substantial manipulation**.

[derived from the US Code of Federal Regulations, 21CFR1271.3(f)(2) [**41**]]

2.197 minor histocompatibility antigen (mH antigen)

naturally polymorphic protein that is recognized as foreign by the immune system of the recipient, potentially contributing to the rejection of a **tissue**

2.198 morula

pre-implantation embryo of about 30 cells produced after cleavage of the **zygote** around 96 hours following fertilization

NOTE 1 The morula is a sphere of **blastomeres** contained within a glycoprotein membrane (zona pellucida).

NOTE 2 See also **blastocyst**.

2.199 multipotent

having the ability to develop into a limited number of cell types

2.200 mycoplasma

parasitic bacterium without a cell wall, which belongs to the phylum Mollicutes

NOTE Mycoplasma is a common **contaminant** in **cell culture** and can cause serious deleterious effects on cells. It is resistant to many antibiotics and as such is hard to remove entirely from a cell culture.

2.201 necrosis

non-programmed cell death

NOTE See also **apoptosis**.

2.202 non-clinical study

study performed ***in vitro*** and/or ***in vivo*** (in animals) to provide data on an **investigational medicinal product**

NOTE See also **preclinical study**.

2.203 non-interventional trial

trial where a **medicinal product** is prescribed in the usual manner in accordance with the terms of the **marketing authorization**

NOTE The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the trial. No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

[derived from European Directive 2001/20/EC [39]]

2.204 observational trial

trial to assess biomedical health outcomes in predetermined groups of individuals where the investigator does not assign specific interventions to the individuals

2.205 off-label use

use of a **medicinal product** to treat a separate medical condition to that which it has been approved for

2.206 open-label trial

randomized trial in which both the clinician and patient are aware of which **arm** of the trial the patient is on

NOTE Contrasts with **single-blind trial** and **double-blind trial**.

2.207 organ

differentiated part of the human body, formed by different **tissues**, that maintains its structure, vascularization and capacity to develop physiological functions with a significant level of autonomy

NOTE A part of an organ is also considered to be an organ if its function is to be used for the same purpose as the entire organ in the human body, maintaining the requirements of structure and vascularization.

[derived from European Directive 2010/45 [4]]

2.208 orphan drug

medicinal product designed to treat a rare disease

2.209 parallel group

treatment and **control** are allocated to different individuals

2.210 parthenogenesis

development of a female embryo without fertilization from the male

2.211 parthenogenetic stem cell line

stem cell line derived from a one-pronuclear oocyte formed following **parthenogenesis**

NOTE Derivation of such a line avoids ethical issues associated with the derivation of human **embryonic stem cells** and also enables the development of homologous **cell lines** suitable for **transplantation**.

2.212 passage

transfer of cells from one **cell culture** environment to another

2.213 passage number

number of times cells have been transferred from one **cell culture** environment to another

2.214 passive surveillance

surveillance conducted by a method that relies on the collection of unsolicited initial patient **safety** information

NOTE 1 Examples include spontaneous reporting schemes, literature monitoring and Internet searches.

NOTE 2 Contrasts with **active surveillance**.

[derived from the European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 9A [12]]

2.215 pathogen

disease-producing agent or microorganism

[Dorland's Pocket Medical Dictionary [31]]

2.216 performance indicator

measurable value used to quantify **quality** objectives to reflect the performance of an organization, process or system

NOTE Also known as performance metrics.

[derived from ICH Harmonised Tripartite Guideline Q10 [42]]

2.217 permitted embryo

embryo licensed for use ***in vitro*** fertilization treatment

NOTE 1 The licensing of permitted embryos is covered by the Human Fertilisation and Embryology Act 1990 (and amendments) [6].

NOTE 2 See also **admixed embryo**.

2.218 pharmacodynamics

study of the biochemical and physiological effects of **medicinal products** and the mechanisms of their actions

[Dorland's Pocket Medical Dictionary [31]]

2.219 pharmacokinetics

study of the fate of drugs in a body

NOTE This includes a mathematical account of their absorption, distribution, metabolism and excretion.

[derived from the Committees on Toxicity, Mutagenicity, Carcinogenicity of Chemicals in Food, Consumer Products and the Environment's Annual Report 2006 [43]]

2.220 pharmacology

study of the uses, effects and actions of **medicinal products** on living systems

2.221 pharmacovigilance

science relating to the detection, assessment, understanding and prevention of adverse effects from medicines

[derived from the World Health Organization's The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products [44]]

2.222 phase I trial

clinical trial performed in patients to determine **safety** data

NOTE Preliminary efficacy data can also be obtained from a phase I trial.

2.223 phase II trial

clinical trial performed in patients to ascertain **safety** and efficacy

NOTE This can be further separated into a phase IIa trial and phase IIb, which determine dosing requirements and efficacy respectively.

2.224 phase III trial

clinical trial that involves a large number of patients in different clinical settings to determine **safety** and efficacy

2.225 phase IV trial

post-authorization **clinical trial** using pharmacovigilance to determine the long-term side effects of medicinal products

2.226 phenotype

physical and biological characteristics of a cell or organism as determined by both genetic make-up and environmental influences

2.227 placebo

product or treatment that mimics a **medicinal product** but contains no **active substance**

2.228 placebo controlled trial

controlled trial in which the **control** is a **placebo**

2.229 placing on the market

first making available in return for payment or free of charge a **medicinal product** with a view to distribution and/or use on the market

[derived from European Directive 90/385/EEC (and amendments) **[10]**]

2.230 plasmid

piece of DNA usually present in a bacterial cell as a circular entity separated from the cell chromosome

NOTE It can be modified by molecular biology techniques, purified out of the bacterial cell and used to transfer its DNA to another cell.

[European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, draft Annex 2 **[26]**]

2.231 plating efficiency

measure of the number of colonies originating from single cells

2.232 pluripotent

having the ability to develop into all cell lineages, except those related to extraembryonic **tissues**

NOTE 1 In humans there are three cell lineages from which all cell types, except extraembryonic tissues (e.g. placenta), are developed. These are the endoderm, mesoderm and ectoderm.

NOTE 2 Contrasts with **unipotent**.

2.233 polymerase chain reaction (PCR)

technique for the ***in vitro*** amplification of a specific target DNA sequence from a background of non-target DNA

2.234 population doubling

measured doubling of cell numbers

2.235 porosity

property of a solid which contains an inherent or induced network of channels and open spaces

NOTE This can be measured by the ratio of the pore (void) volume to the apparent (total) volume of a porous material and is commonly expressed as a percentage.

[ASTM F2312-11]

2.236 post-authorization safety study

study relating to an authorized **medicinal product** conducted with the aim of identifying, characterizing or quantifying a **safety** hazard, confirming the safety profile of the **medicinal product**, or of measuring the effectiveness of **risk management** measures

NOTE This can be one element in a **phase IV trial**.

[Directive 2001/83/EC (and amendments) [1]]

2.237 post-market surveillance

practice of monitoring the **safety** or efficacy of a **medicinal product** or **medical device** after it has been released onto the market

NOTE 2 See also **clinical follow-up**.

2.238 potency

<**medicinal product**> quantitative measure of biological activity based on those attributes of a product that are linked to relevant biological properties

[derived from ICH Harmonised Tripartite Guideline Q6B [45]]

<stem cell> extent to which a stem cell can differentiate along distinct cell lineage pathways

NOTE For example, whether a stem cell is **multipotent** or **pluripotent**.

2.239 power of study

<statistics> number or percentage that indicates the probability a study will obtain a statistically significant effect

2.240 preclinical study

study performed ***in vitro*** and/or ***in vivo*** (in animals) to provide data to support initiation of **clinical trial** phases and/or support **marketing authorization**

NOTE See also **non-clinical study**.

2.241 precursor cell

cell at a stage of development immediately prior to terminal **differentiation**

NOTE See also **progenitor cell** and **somatic cell**.

2.242 preservation

prevention or retardation of the biological or physical deterioration of cells or **tissues**

NOTE 1 This can be achieved during cell or **tissue processing**, for example, through the use of chemical agents or alterations in environmental conditions.

NOTE 2 See **cryopreservation**.

[derived from European Directive 2004/23/EC [2]]

2.243 primary cell culture

culture of cells isolated directly from **tissue**

2.244 principal investigator

investigator who takes overall charge at a **clinical trial** centre

NOTE See **chief investigator** and **clinical investigator**.

2.245 process analytical technology (PAT)

system for designing, analysing and controlling **manufacturing** through timely measurements, during processing, of critical **quality** and performance attributes of raw and in-process materials and processes with the goal of ensuring final product **quality**

[ICH Harmonised Tripartite Guideline Q8(R2) [46]]

2.246 progenitor cell

cell which is at a more advanced stage of **differentiation** than a **stem cell** but is not yet fully differentiated

NOTE See also **precursor cell** and **somatic cell**.

2.247 proliferation

growth of a cell population by **cell division**

2.248 prospective trial

clinical trial that observes outcomes during a trial and relates these to influencing factors

NOTE 1 Influencing factors include suspected **risk** or protection factors.

NOTE 2 Contrast with **retrospective trial**.

[derived from The Oxford Dictionary of Statistical Terms [47]]

2.249 protein expression

translational and post-translational processing of proteins

2.250 protocol

<**clinical trial**> document that describes the objectives, design, methodology, statistical considerations and organization of a **clinical trial**

NOTE The term protocol refers to the protocol, successive versions of the protocol and protocol amendments.

[derived from European Directive 2001/20/EC [39]]

2.251 provenance

adequate knowledge of the source of a material, cells or reagents used in the derivation of cells in order for a **risk** assessment of **contamination** or infection to be made

NOTE 1 Provenance is essential when a material, cells or reagents are intended for clinical use.

NOTE 2 Provenance can include knowledge of the medical histories of **donors** of gametes used to derive embryos.

2.252 purity

level of freedom from **impurities**

2.253 qualification

<**manufacturing**> confirmation by examination and provision of objective evidence that equipment functions in the manner intended by the manufacturer

NOTE 1 This includes examination of the installation, operation and performance of equipment.

NOTE 2 See also **validation**.

2.254 qualified person (QP)

person responsible for certifying that a **batch** of **medicinal product** conforms to requirements prior to release

NOTE European Directive 2001/83/EC [1] specifies requirements for a QP.

2.255 qualified person responsible for pharmacovigilance (QPPV)

person responsible for **pharmacovigilance** for licensed **medicinal products**

NOTE European Directive 2001/83/EC [1] specifies requirements for a QPPV.

2.256 quality

degree to which a set of inherent properties of a product, system or process fulfils requirements

[ICH Harmonised Tripartite Guideline Q9 [48]]

2.257 quality assurance (QA)

total sum of organized arrangements made with the object of ensuring that **medicinal products** are of the **quality** required for their intended use

[derived from the European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, Part I, Chapter 1 [49]]

2.258 quality by design (QbD)

systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality **risk management**

[ICH Harmonised Tripartite Guideline Q8(R2) [46]]

2.259 quality control (QC)

process or set of processes or measures used to maintain predefined standards to assure the **quality** of a product

2.260 quality system

documented organizational structure, defined responsibilities, procedures, processes and resources for implementing **quality** management including all activities which contribute to **quality**, directly or indirectly

[derived from European Directive 2006/17/EC [33]]

2.261 quiescence

stage in a cell cycle when the cell stops dividing

2.262 randomized trial

trial in which participants are randomly (i.e. by chance) assigned to one of two or more treatment **arms** of a **clinical trial**

NOTE Examples include **double-blind trial**, **open-label trial** and **single-blind trial**.

2.263 raw material

starting materials, reagents and solvents intended for use in the production of **intermediates** or an **active substance**

[derived from the European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, Part II [9]]

2.264 real time release testing (RTR testing)

evaluation and ensurance of the **quality** of an in-process product and/or final product based on process data

NOTE Process data typically include a combination of measured material attributes and process controls.

[derived from ICH Harmonised Tripartite Guideline Q8(R2) [**46**]]

2.265 recall

removal or correction of a marketed product that a relevant authority considers to be in violation of their laws

2.266 regenerative medicine

process of replacing or regenerating human cells, **tissues** or **organs** to restore or establish normal function

[derived from Regenerative Medicine, 2008, 3(1), 1–5 [**50**]]

2.267 release criteria

predetermined criteria against which a product is assessed to determine its suitability for release

NOTE These measurements can include identity, **purity**, impurities, sterility, **potency**, **cell viability** and total cell number.

[derived from the European Medicines Agency's Guideline on Human Cell-Based Medicinal Products [**22**]]

2.268 reproductive cloning

production of identical animals via **cloning**

2.269 reprogramming

<genetics> facilitating the uptake of genes by a cell

NOTE This is a method frequently used to derive **induced pluripotent stem cells (iPS cells)**.

2.270 retrospective trial

clinical trial that identifies outcomes from data that has previously been collected and relates these to influencing factors

NOTE 1 Influencing factors include suspected **risk** or protection factors.

NOTE 2 Contrast with **prospective trial**.

[derived from The Oxford Dictionary of Statistical Terms [47]]

2.271 risk

combination of the probability of occurrence of harm and the severity of that harm

[ISO/IEC Guide 51:1999]

NOTE See also **risk analysis** and **risk management**.

2.272 risk analysis

systematic use of available information to identify hazards and to estimate the **risks**

NOTE Risk analysis includes examination of different sequences of events that can produce hazardous situations and harm.

[ISO/IEC Guide 51:1999]

2.273 risk management

systematic application of management policies, procedures and practices to the tasks of analysing, evaluating and controlling **risk**

[BS EN ISO 14971:2009, 2.22]

NOTE Attention is drawn to the European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 9A **[12]**, which in the context of **pharmacovigalance**, specifically defines:

a risk management system as a set of **pharmacovigilance** activities and interventions designed to identify, characterize, prevent or minimize risks relating to **medicinal products**, and the assessment of the effectiveness of those interventions;

EU risk management plan (EU-RMP) as a document that describes a risk management system, which is specific to a particular product; and

risk minimization as activities used to reduce the probability of an **adverse reaction** occurring or its severity should it occur.

2.274 safety

freedom from unacceptable **risk**

[ISO/IEC Guide 51:1999]

2.275 safety follow-up

systematic collection and collation of data that is designed in a way that enables learning about the **safety** of a **medicinal product**

NOTE It can include **active surveillance**, **clinical trials**, **observational trials** and **passive surveillance**.

[European Medicines Agency's Guideline on safety and efficacy follow-up – Risk management of advanced therapy medicinal products **[24]**]

2.276 same surgical procedure

surgical intervention, or series of interventions, related to the same therapeutic goal on an individual under the continuous care of a medical doctor or team of medical doctors for the purpose of obtaining a specific therapeutic effect

2.277 scaffold

support, delivery vehicle or matrix for facilitating the migration, binding or transport of cells or **bioactive agents**

[derived from ASTM F2312-11]

2.278 scale out (or scale horizontally)

increasing production by an increase in the number of units rather than increasing the size of the process

2.279 scale up (or scale vertically)

increasing the size of the process rather than increasing production by an increase in the number of units

2.280 seeding density

number of cells used to initiate or progress a **cell culture**

NOTE Usually expressed as total number of cells per unit area or volume.

2.281 self-renewal

ability to continuously undergo **cell division** where each daughter cell is identical

2.282 senescence

decline or degeneration related to cellular ageing

2.283 sensitivity

<statistics> degree of response to a change in input/components of the test

2.284 serious adverse event (SAE)

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 that might result in, or prolong, hospitalization or morbidity

NOTE 1 A legal definition applicable in the EU for clinical trials is given in Table A.1.

NOTE 2 See also **adverse event**.

[European Directive 2004/23/EC [2]]

2.285 serious adverse reaction (SAR)

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, hospitalization or morbidity

NOTE 1 A legal definition of SAR applicable in the EU for clinical trials is given in Table A.1.

NOTE 2 See also **adverse reaction** and **unexpected adverse reaction (UAR)**.

[European Directive 2004/23/EC [2]]

2.286 sham procedure

procedure that is performed as a **control** and that is similar to but omits a key therapeutic element of the treatment or procedure under investigation

2.287 side effect

undesired action or effect resulting from therapeutic treatment

2.288 significance

<statistics> fixed probability of wrongly rejecting the null hypothesis

2.289 single-blind trial

randomized trial in which either the clinician or patient are unaware of which **arm** of the trial the patient is on

NOTE 1 See also **double-blind trial**.

NOTE 2 Contrasts with **open-label trial**.

2.290 somatic cell

fully differentiated cell from an adult body or fetus

NOTE 1 These cells can be **autologous**, **allogeneic** or **xenogeneic somatic cells** that have been manipulated or altered ***ex vivo*** to be administered in humans to obtain a therapeutic, diagnostic or preventive effects.

NOTE 2 See also **progenitor cell** and **precursor cell**.

[derived from the UK Stem Cell Bank's Code of Practice for the Use of Human Stem Cell Lines [13]]

2.291 somatic cell nuclear transfer (SCNT)

technique that combines an enucleated egg (nucleus removed) and the nucleus of a somatic cell to make an embryo

2.292 somatic cell therapy medicinal product

biological medicinal product which contains or consists of cells or **tissues** that have been subject to **substantial manipulation** so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or **tissues** that are not intended to be used for the same essential functions in the recipient and the **donor**; and is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues

NOTE The manipulations listed in Annex I to European Regulation No. 1394/2007 [5], in particular, are not considered as substantial manipulations.

[Directive 2001/83/EC (and amendments) [1]]

2.293 specification

predetermined set of criteria to which a **medicinal product**, **active substance** or **intermediates** thereof, should conform to be considered acceptable for its intended use

[derived from ICH Harmonised Tripartite Guideline Q6B [45]]

2.294 specificity

<statistics> probability of a true negative being correctly identified

NOTE Contrasts with **false negative**.

2.295 stability testing

determination of the shelf life of a substance under anticipated storage and in use

NOTE 1 This includes, for example, assessment of the ability of cells to survive and maintain their **potency**.

NOTE 2 This applies to, for example, **raw materials**, **starting materials**, **intermediates** and final products.

[derived from the European Medicines Agency's Guideline on Human Cell-Based Medicinal Products [22]]

2.296 standard operating procedure (SOP)

detailed, written instructions to achieve uniformity of the performance of a specific function

[ICH Harmonised Tripartite Guideline E6(R1) [51]]

2.297 starting material

raw material, **intermediate** or **active substance** that is used in the production of an active substance and that is incorporated as a fragment into the structure of the active substance

NOTE 1 Attention is drawn to European Directive 2001/83/EC (and amendments) [1], Annex 1, Part IV, which requires for **somatic cell therapy medicinal products** and **tissue engineered products** that additional substances (e.g. **scaffolds**, matrices, devices, **biomaterials**, **biomolecules** and/or other components) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.

NOTE 2 See also **cellular starting material**.

[derived from ICH Harmonised Tripartite Guideline Q7 [11]]

2.298 state of control

condition in which a set of controls consistently provides assurance of continued process performance and product **quality**

[derived from ICH Harmonised Tripartite Guideline Q10 [42]]

2.299 stem cell

cell capable of both **asymmetric cell division** and **self-renewal**, and of providing cells capable of **differentiation**

2.300 stem cell line

cell line consisting of **stem cells**

2.301 sterile

completely absent of any viable microorganisms

NOTE Sterility is determined through a validated process that demonstrates the absence of microorganisms at a specified statistical probability.

2.302 stromal cells

non-haematopoietic cells capable of supporting the growth of blood cells

NOTE Typically derived from bone marrow.

2.303 subject

individual who participates in a **clinical trial** as either a recipient of the **investigational medicinal product** or **control**

[derived from European Directive 2001/20/EC [39]]

2.304 substantial manipulation

manipulation of cells or **tissue** so that biological characteristics, physiological functions or structural properties relevant for the therapeutic application are achieved

NOTE 1 The following manipulations are not considered as substantial manipulations: cutting; grinding; shaping; centrifugation; soaking in antibiotic or antimicrobial solutions; sterilization; irradiation; cell separation, concentration or purification; filtering; lyophilization; freezing; **cryopreservation**; and **vitrification**.

NOTE 2 Contrasts with **minimal manipulation**.

[derived from European Directive 2001/83/EC (and amendments) [1]]

2.305 syngeneic

where **donor** and recipient are genetically identical individuals

NOTE For example, identical twins or animals of a single highly inbred strain.

2.306 therapeutic cloning

production of cells that exactly match the cells of a **donor**

2.307 therapeutic immunosuppression

suppression of the immune response in order to prevent the rejection of grafts or transplants or control autoimmune diseases

2.308 therapy

treatment intended to heal or relieve a disorder

2.309 tissue

aggregation of specialized cells united in the performance of a particular set of functions

[derived from ASTM F2312-11]

2.310 tissue bank

collection of **tissues** stored for research or clinical utility

2.311 tissue engineered product

product that contains or consists of **engineered cells and/or tissues**, and is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human **tissue**

[European Regulation No. 1394/2007 [5]]

2.312 tissue engineering

use of a combination of cells, engineering, materials and methods to **manufacture *ex vivo*** living **tissues** and **organs** that can be implanted to improve or replace biological functions

NOTE Usually through the use of **scaffolds** for restoration or regeneration of tissues or organs.

2.313 tissue establishment

establishment where the activities of processing, **preservation**, storage or distribution of human **tissue** and cells are undertaken

NOTE 1 For example, a **tissue bank** or a unit of a hospital.

NOTE 2 It might also be responsible for procurement or testing of tissue and cells.

[derived from European Directive 2004/23/EC [2]]

2.314 tissue typing

process of determining the set of **human leucocyte-associated antigens** encoded within an individual's **major histocompatibility complex**

NOTE This is performed in order to determine the acceptance or rejection of a **tissue** graft prior to **transplantation**.

2.315 toxicology

study of the potential of materials to harm health by virtue of their effect on biological systems

2.316 totipotent

having the ability to develop into all types of cell including extraembryonic **tissues**

NOTE An example of extraembryonic tissue is placenta.

2.317 traceability

ability to track **tissues** or cells by recording their status at all points from initial collection right through to either **transplantation** or disposal

NOTE Legal definitions applicable in the EU and USA are given in Table A.1.

2.318 transgenic

organism that contains a foreign gene in its normal genetic component

NOTE Such organisms might be produced in order to express biological pharmaceutical materials.

[derived from the European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, draft Annex 2 **[26]**]

2.319 transgenic human embryo

admixed embryo created by inserting animal genes into an early embryo

[derived from the Human Fertilisation and Embryology Authority's report on hybrids and chimeras **[14]**]

2.320 translation

active turning of a basic science discovery into a safe and effective **therapy** deployed in routine clinical practice

2.321 transplantation

process of implanting cells, **tissues** or **organs**

[derived from ASTM F2312-11]

2.322 transplantation tolerance

state of induced immunological acceptance of a graft that would otherwise be rejected

2.323 trophoblast

outer cell layer of a **blastocyst**

NOTE It develops into extraembryonic tissue, such as placenta.

[derived from the Stem Cell Information Glossary [20]]

2.324 tumour

swelling of a part of the body caused by an abnormal growth of **tissue** whether benign or malignant

2.325 tumour-associated antigen

protein whose expression is predominantly restricted to a given type of **tumour**

NOTE This can serve as a target for a **cancer vaccine**.

2.326 tumorigenicity

tendency of cells to form a **tumour**

2.327 unexpected adverse reaction (UAR)

adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics

NOTE See also **adverse reaction** and **serious adverse reaction (SAR)**.

[derived from European Directive 2001/83/EC (and amendments) [1]]

2.328 unipotent

having the ability to develop into only one cell type

NOTE Contrasts with **pluripotent**.

2.329 upstream processing

technologies involved in the initial stages of product **manufacture**

NOTE 1 For example where cells are grown in a **bioreactor**.

NOTE 2 Contrasts with **downstream processing**.

2.330 user requirement brief (URB)

overarching, strategic document describing what outcomes an end user expects from a project as a whole

NOTE 1 It includes a description of the business, as well as the technical, need for a project.

NOTE 2 It is used, for example, for capital manufacturing projects licensed by a relevant **competent authority**, such as the Medicines and Healthcare products Regulatory Agency (MHRA).

NOTE 3 It is underpinned by **user requirement specifications (URSs)**.

2.331 user requirement specification (URS)

document describing what outcomes an end user expects from an individual component of a project

NOTE 1 Individual components of a project include individual products and systems.

NOTE 2 It is written in line with the requirements of a **user requirement brief (URB)**.

2.332 validation

means of establishing documented evidence that provides a high degree of assurance that a specific process, **standard operating procedure**, piece of equipment or environment will consistently produce a product meeting its predetermined **specifications** and **quality** attributes perform according to the intended specified outcomes

NOTE A process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use.

[European Directive 2006/17/EC [33]]

2.333 vector

agent that can carry a DNA fragment into a host cell

NOTE If it is used for reproducing the DNA fragment, it is named **cloning** vector. If it is used for expressing the fragment, it is named expression vector.

2.334 viral vector

vector derived from a virus and modified by means of molecular biology techniques in a way as to retain some, but not all, the parental virus genes

NOTE If the genes responsible for virus replication capacity are deleted, the vector is made replication-incompetent.

[European Commission's Eudralex: The Rules Governing Medicinal Products in the European Union, Volume 4, draft Annex 2 [26]]

2.335 vitrification

form of **cryopreservation** whereby cells, **tissues** or **organs** are converted into a glass-like amorphous state prior to cooling to ultra-low temperatures

2.336 whole bioprocessing

<**allogeneic**> entire bioprocess from **donor** through to implantation of a **cell therapy**
<**autologous**> entire bioprocess from patient biopsy through to implantation of a **cell therapy**

2.337 working cell bank (WCB)

cell bank prepared from aliquots of a homogeneous suspension of cells obtained from culturing cells from the **master cell bank**

[derived from ICH Harmonised Tripartite Guideline Q5D [21]]

2.338 xenogeneic

where the **donor** and recipient belong to different species

[derived from ASTM F2312-11]

2.339 xenograft

xenogeneic graft

2.340 xenotransplantation

procedure that involves the **transplantation** or infusion into a human recipient of either cells, **tissues** or **organs** from a non-human animal source, or human body fluids, cells, **tissues**, or **organs** that have had ***ex vivo*** contact with live non-human cells, **tissues**, or **organs**

[ASTM F2312-11]

2.341 zygote

fertilized egg

ANNEX A (INFORMATIVE) REGULATORY TERMS

Table A.1 – Regulatory terms

Table A.1 – Regulatory terms.

Term	Definition	Legislation
Adverse event	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment	European Directive 2001/20/EC [39]
Adverse experience	Adverse event associated with the use of a biological product in humans, whether or not considered product related, including the following: an adverse event occurring in the course of the use of a biological product in professional practice; an adverse event occurring from overdose of the product whether accidental or intentional; an adverse event occurring from abuse of the product; an adverse event occurring from withdrawal of the product; and any failure of expected pharmacological action	US Code of Federal Regulations, 21CFR600.80 [52]
Adverse reaction	Untoward and unintended responses to an investigational medicinal product related to any dose administered	European Directive 2001/20/EC [39]
	Response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function	Directive 2001/83/EC (and amendments) [1]

Table A.1 – Regulatory terms.

Term	Definition	Legislation
Clinical trial	Investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy	European Directive 2001/20/EC [39]
	Prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices)	US National Institutes of Health Glossary & Acronym List [53]
Ethics committee	Independent body in a Member State, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent	European Directive 2001/20/EC [39]
	Review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection	US Code of Federal Regulations, 21CFR312.3 [54]

Table A.1 – Regulatory terms.

Term	Definition	Legislation
Human admixed embryo	An embryo created by replacing the nucleus of an animal egg or of an animal cell, or two animal pronuclei, with: two human pronuclei; one nucleus of a human gamete or of any other human cell; or one human gamete or other human cell; any other embryo created by using: human gametes and animal gametes; orone human pronucleus and one animal pronucleus; a human embryo that has been altered by the introduction of any sequence of nuclear or mitochondrial DNA of an animal into one or more cells of the embryo; a human embryo that has been altered by the introduction of one or more animal cells; or any embryo not falling within paragraphs (a) to (d) which contains both nuclear or mitochondrial DNA of a human and nuclear or mitochondrial DNA of an animal ("animal DNA") but in which the animal DNA is not predominant	Human Fertilisation and Embryology Act 1990 (and amendments) [6]
Informed consent	Decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation	European Directive 2001/20/EC [39]
	Person's voluntary agreement, based upon adequate knowledge and understanding, to participate in human subjects research or undergo a medical procedure	US National Institutes of Health Glossary & Acronym List [53]
Serious adverse event (SAE) or serious adverse reaction (SAR)	Untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect	European Directive 2001/20/EC [39]

Table A.1 – Regulatory terms.

Term	Definition	Legislation
Traceability	Ability to locate and identify the tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal, which also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/cells to the recipient(s); traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells	European Directive 2006/17/EC [33]
	Establishment and maintenance of procedures for identifying with a control number each unit or batch of finished medical devices and where appropriate components	US Code of Federal Regulations, 21CFR820.65 [55]

ANNEX B (INFORMATIVE) FINANCE

B.1 angel investor

specialist, independent investor that typically provides start-up capital to early stage companies

B.2 cash burn rate

measure of how rapidly a company spends its shareholders' capital

B.3 cross licensing

reciprocal agreement between two or more parties that confers rights to access and utilized named intellectual capital

B.4 discount rate

interest rate applied in **discounted cash flow analysis** to determine the time value of money, accounting for inflation and predicted returns from alternative investments

B.5 discounted cash flow (DCF) analysis

valuation technique that accounts for the time value of money, including inflation and predicted returns from alternative investments

B.6 disruptive technology

innovation that creates a new (and unexpected) market by applying a different set of values

B.7 initial public offering (IPO)

transaction whereby a company offers shares of ownership, or equity, to investors through a market in order to raise capital

NOTE Thereafter, the shares can be publicly traded without any restrictions on ownership.

B.8 internal rate of return (IRR)

discount rate at which the **net present value (NPV)** of costs, negative cash flows become equal to the **NPV**, of benefits, positive cash flows, of a given investment

NOTE In other words, the point at which any profits generated by a company exceed the borrowing costs of capital used to provide the initial investment. Calculated through **discounted cash flow (DCF) analysis**.

B.9 net present value (NPV)

valuation methodology that analyses discounted cash flows to account for their present and future values

B.10 parallel importing

importing and sale of pharmaceutical products into jurisdictions other than those in which they were initially intended for sale, thus attempting to realize an arbitrage opportunity

B.11 private equity

investment in or acquisition of mature companies

B.12 small & medium sized enterprise (SME)

companies with headcount and either turnover or balance sheet total below certain limits

NOTE 1 A small enterprise is described as having a headcount of below 50 and a turnover of less than or equal to €10 000 000.

NOTE 2 A medium enterprise is described as having a headcount of below 250 and a turnover of lower than or equal to €50 000 000.

B.13 venture capital

investment in or acquisition of early stage companies

[US Food And Drug Administration's Guidance for Industry – Process Validation: General Principles and Practices [**30**]]

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