Human cell- and tissue-based products: Progress, promise and regulatory issues

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Abstract The field of cell- and tissue-based products is radically changing through the use of biotechnology. The authors outline developments that are currently taking place, leading to the need for adapted regulations, for which worldwide harmonisation is important since potential safety issues have no borders and companies operate globally. Potential ethical issues need to be discussed and resolved within society in an open and transparent way.

Keywords: cell therapy, ethics, harmonisation, safety, worldwide regulatory framework

Introduction

Many human cell- and tissue-based products are currently being classified as medical devices, others as biologicals, and the remaining ones do not belong to an existing category. The market for these products is very heterogeneous, highly segmented and still poorly recognised as a high-technology sector producing quality treatments for many patients suffering from life-threatening or seriously debilitating conditions. The field is currently undergoing radical changes, not least by the use of new biotechnology-derived solutions within existing applications, as well as by the creation of totally new treatment concepts for major human health problems. Indeed, the advent of biological solutions to many medical problems traditionally covered by medical devices is leading to an increasing number of products that have fallen between regulations, and is creating totally new fields, such as the emerging field of biosurgery. These radical changes are no more evident than in the case of products that are manufactured from or composed of human tissue. There are an increasing number of such innovative human tissue products being developed with a variety of healthcare applications, from prosthetic and restorative to therapeutic or even cosmetic in nature. However, the introduction of this new class of products into the market-place has been difficult because of the lack of harmonised regulations, even within Europe. In this paper, we outline some of the developments that are currently taking place to underscore these changes, as well as the resulting need in new or adapted regulations worldwide.

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Genzyme's experience with Carticel® (autologous cultured chondrocytes) and Epicel® (cultured epidermal autografts) has proven the concept that cultured cells can replace some function lost to injury or disease. The company is also developing several other cellular-based therapies, including additional autologous cell therapies, cancer vaccines, gene therapy and xenografts, and therefore its base of expertise in this field makes it of importance that, as a responsible player, the company is proactively involved in the debate about regulating this new field.

In the current decade, advances in medical technology will continue to progress dramatically, and many existing and new players from industry will develop many more tissue-based products. The availability of these innovations to patients, and their potential to provide advantages over currently available treatments, rest not only with researchers and industry, but finally with the regulatory framework which needs to take the boundary-crossing nature of many of these new products into account. Cell- and tissue-based medical products and services are currently subject to a wide variety of regulatory oversight in European member states, including considerations such as whether the product source is autologous or allogeneic, whether it is processed, stored or used for a homologous function, and whether the cells or tissues have a metabolic or reproductive function.

Current regulatory frameworks

USA

In February 1997, the US Food and Drug Administration (FDA) published the Proposed Approach[1] to the Regulation of Cellular and Tissue-Based Products. The document laid the groundwork for a flexible approach to the regulation of products in the USA, based on the level of concern they pose to public health. While the FDA has provided a thorough review of products brought to its attention, the lack of overall regulatory framework has presented problems. It has been three years since the publication of the Center of Biologics Evaluation and Research (CBER) Proposed Approach and recently a number of guidelines have been issued from a number of sources for cell and tissue products that apply all or in part to both human- and animal-derived cells and tissues. These include new regulations on establishment registration and product listing,[2] a final Public Health Service guideline on xenotransplantation[3] and a draft guidance for the use of xenotransplantation products in humans from the CBER,[4] proposed regulations defining good tissue practice (GTP)[5] and finally, a draft United States Pharmacupoeia (USP) chapter dedicated to cell therapies.

Manufacturers of drug and biological products that are subject to marketing clearance by the FDA are required to demonstrate that the product is safe, and has the identity and strength, and meets the quality and purity characteristics that it is represented to possess. The FDA used experience gathered during its review of licence applications and subsequent facility inspections to issue a guidance document that can now be used by manufacturers of cell-based products. Guidance documents should also be developed in advance of the next generation products so that the learning experience for the first company is not so great as to discourage companies from being pioneers.

The Proposed Approach specifies that for more than minimally manipulated cell and tissue products clinical efficacy should be demonstrated. The phrase 'more than minimally manipulated' has been interpreted broadly by the FDA so that virtually any processing of cells includes the product in this category. Even a simple expansion of the cell population is considered more-than-minimal manipulation. Another topic being discussed is that preclinical animal models can also be very challenging for these cell-based products: many animals have sufficiently different anatomical and physiological characteristics from humans that make extrapolation to the human condition difficult.

Some of the newer cell and tissue engineered products have presented unique potential safety issues, such as the need for testing for porcine retrovirus in xenografts. To ensure proper safety testing in this case, the FDA, National Institutes of Health (NIH) and industry are working together to develop appropriate assay methods and a patient-surveillance algorithm.[6,7]

European Union

There are currently no pan-European regulations for the control of quality, safety and efficacy of human tissue-based products – whether they be autologous, allogeneic or xenogeneic in nature. Discussions to achieve this have been delayed by terminology and ethical issues among member states. On the level of the member states, some have worked out advanced programmes related to those products.

Sweden has become the only European state to date to make a classification of human tissue-based products as medicinal products, according to the regulations 65/65/EEC *et al*. This definition has led to numerous discussions with the regulatory authority as to the applicability of associated guidelines and regulations for medicinal products. Other European states, such as the UK, Ireland and Denmark, have indicated that tissue-based products are outside the scope of either medicinal product or medical device legislation, and hence are 'un-regulatable'. In these instances, companies can commercialise product at will, with no approvals necessary apart from import licences, prior to supply to the customer.

In between these two extremes, European member states employ a myriad of national regulations, without any recognisable base for harmonisation. Spain requests that product is 'brokered' by third party tissue services foundations, who effectively act as quality control for import of products, without physically testing the material. In Germany, tissue products are classified as 'unfinished drugs', and therefore are not subject to submissions to the central regulatory authority BfArM. Instead, a company must 'apply the spirit' of the German drug law (including good manufacturing products and import permissions), while individual *Länder* within Germany may exert local restrictions. Further individual regulations are in development within France and Italy.

The lack of pan-European regulation is making the commercialisation of tissue products very complex, as no centralised approval or marketing strategy can be developed. This results in either delay in availability of such products to patients, or puts their safety at risk, where no regulations are applicable. The picture is made even more complicated by the requests for evidence of cost-effectiveness by some reimbursement authorities: 'un-regulatable' does not exclude a review from a pharmaco-economics perspective.

Recently, the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMEA) has issued a 'Points to Consider' document',[8] which has suggested that all member states should regulate human tissue products as a medicinal product, while medical device regulators in Europe have been working on a parallel track to develop a European Directive for human tissue-based products, separate from medicinal products as well as from *in vitro* diagnostic products.

New product categories in development

In this section, some of the new areas developing by using cell and tissues from human origin are emphasised. This exemplifies even further the need for a regulatory framework.

Cardiac cells

Several research groups, both academic and commercial (including Genzyme), are developing a cellular therapy to treat heart tissue damaged by myocardial infarction (MI).

Although there are many well-established treatments for MI patients, no therapy exists for restoring function to a heart damaged by large myocardial infarct. According to the American Heart Association,[9] there are over one million acute MIs per year that account for approximately 250,000 deaths per year in the USA. Many patients surviving an acute MI will require prolonged medical therapy. Approximately 10 per cent of these surviving patients will develop congestive heart failure (CHF) within one year. By restoring function and/or arresting the subsequent decline in heart functions, it is hoped that this new cellular therapy will delay or prevent the onset of CHF in this patient population, providing a treatment option for some patients.

MI results in necrosis of local cardiac muscle and leads to regional scar formation. The resulting scar tissue is structurally unstable and, over time, thins and dilates, impairing cardiac function in that part of the heart. This partial insufficiency often initiates a chain of events within the remaining active muscle, resulting in global maladaptive ventricular remodelling, which means that the remaining viable muscle attempts to remodel itself to compensate for the damaged tissue and loss of function, thereby potentially altering the size of the heart. Rather than compensating, this remodelling exacerbates the cardiac insufficiency stemming from the original injury, causing the cycle to repeat. Cellular therapy to arrest scar expansion and maladaptive ventricular remodelling, specifically autologous cell transplantation therapy, has been proposed as a possible means by which the damaged heart tissue might be stabilised and functionally repaired. Many investigators have studied transplantation of cells into cardiac scar tissue. Most early animal studies support the concept that cultured cells, taken from the heart of the same animal into which they are to be transplanted, survive in myocardial scar tissue, limit scar expansion and improve the function of infarcted hearts. Development of such cellular therapies to restore cardiac function in MI patients is still in the preclinical stage. However, given its promise, it could progress quickly through human clinical trials.

As for other cellular therapies, significant hurdles exist in bringing such cardiac cell therapy to market. The lack of harmonised tissue regulations and standards provides an additional stumbling block for sponsors to assess the available market accurately or to determine the data packages necessary to support product marketing approval in different regions in the world, and is making research and development in this area more difficult.

Xenografts

Therapies based on animal cells and tissues may provide an alternative approach to treat hitherto untreatable conditions. Non-viable animal tissue such as pig heart valves and bone has been used for many years, offsetting limited supply of human equivalents. More recently, additional efforts have been directed towards utilising viable animal tissues for treatments of humans. In degenerative diseases, cell replacement has the potential to restore and/or repair certain body functions. For example, human fetal cells transplanted into the human brain are being studied as a promising emerging therapy for Parkinson's disease. However, while ethical questions, availability of human fetal tissue and many technical hurdles limit the application of this technique, xenografts based on animal tissue may provide a viable alternative. Additional potential applications of xeno-cells include extracorporeal liver assist systems in which pig hepatocytes may provide a temporary support to help patients bridge the time needed before a liver is available for transplantation, or allow the patient's own liver to regenerate. Finally, the success of solid organ transplantation to treat those in end stage renal, liver and cardiac failure, has led to a continuously increasing demand for human donor organs. Transplant waiting lists include more than 180,000 patients worldwide, of whom less than a third will receive the organ they so desperately need.

Xenotransplantation may offer a solution to this dilemma.[10]

The US FDA calculates an average of 29 people per year receive xenotransplantations in clinical trials and expects this rate will remain steady over the next five years.[11] On the other hand, the potential risk for cross-species transmission of infectious agents to patients, their close contacts and the general public continues to be debated. Concerns arising from the threat of xenozoonoses form the basis of current approaches to the regulation of xenografts.

The new millennium has brought some encouraging changes in the xenocell therapy regulatory landscape, most notably the progress in Europe and the will to harmonise on a global scale. Where previous debates focused solely on the ethics and conduct of clinical trials, current discussions address the reality that clinical trials using xenografts are underway. In October 2000, the Organization for Economic Cooperation and Development (OECD) and the World Health Organization (WHO), supported by the Government of Canada, hosted the Joint WHO/OECD Consultation on Xenotransplantation Surveillance in Paris, France. This meeting included 60 policy makers, medical researchers, clinicians, industry representatives and epidemiologists to discuss possible global approaches to xenotransplantation surveillance. An accepted universal definition of terms, eg a xenotransplantation product, close contact, adverse event, needs to be developed, with a goal of establishing systems to monitor xenotransplant patients and close contacts. Where possible, efforts should be made to align with existing systems as well, and to consider the cost of such systems and the impact on the economy as an additional element of importance. The main objectives of international xenotransplantation surveillance agreed at the Paris meeting are: (1) to rapidly detect and report an infectious disease event, particularly a rare event, should it occur; (2) to share information and cooperate; and (3) to facilitate xenogeneic disease event verification and response coordination. These objectives could be accomplished using existing (and perhaps expanded) links and systems, and not by creating new, burdensome ones. Efforts also continue in refining the xenotransplantation guidelines.

The EMEA, the UK Medicines Control Authority's (MCA) xenotransplantation advisory body and the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) are also actively seeking to complete guidance on patient surveillance. The EMEA recently published a paper[12] recommending that a CPMP Points to Consider be prepared on the use of xenogeneic cell-based therapies by the end of 2001, and indicating that an 'experts meeting' can be expected. The Points to Consider would cover public health issues including quality issues, preclinical development, human clinical safety and efficacy, including follow-up with recipient close-contacts, tissue archives and surveillance.

In the USA, the FDA has piloted a national database for monitoring adverse events and other information from xenotransplantation clinical trials. Sponsors of ongoing xenotransplantation trials in the USA have set up surveillance systems based on the Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation,[13] first issued in 1996. This document outlines recommendations for procedures intended to reduce the risk of transmission of infectious agents to recipients and their contacts through an elaborate cross-reference system of xenotransplantation product recipient, xenotransplantation product, source animal(s), procurement facilities, etc.

A final version of the PHS Guideline was issued in January 2001 and serves to publish a number of positions and guidelines that have already been imposed upon xenotransplantation sponsors. The expanded definition of xenotransplantation herein includes any *ex vivo* contact with human tissue, as first unveiled in 'Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans'.[14] Linked to this expanded definition is the FDA's suggestion of a tiered

approach to regulation of xenotransplantation products to define degrees of risk and levels of surveillance appropriate to that risk. Other agencies are considering this approach to classifying xenotransplantation, including UKXIRA whose 'Report of Infectious Surveillance Steering Group of the UKXIRA'[15] will contain annexes on 'graduated risk' by xenotransplantation classification.

The focus of the now numerous xenotransplantation guidelines, policies and regulations appears to remain on the development and clinical study of xenografts. It is not clear how these criteria will be applied to approved xenogeneic products, and, with some xenotransplantation trials currently in Phase II /III, it is critical that plans be made to bring approved xenogeneic cell-based products to market. The current example of the USA sets up a network of controls on animals, products, recipients and accounts for close contacts, and recognises the potential transient nature of these close contacts. International efforts to harmonise xenotransplantation should be aimed at the development of reasonable and appropriate methods in recognition of a growing body of evidence and experience regarding the safety of this therapy, and be framed within existing public health monitoring and surveillance systems.

Cell-based cancer immunotherapy

Harnessing the body's immune system to fight cancer has been an active area of investigation among physicians and scientists for decades. Thus far, success has been sporadic and unpredictable, though reproducible results in specific diseases such as advanced renal cell carcinoma have served as proof of principle for the entire field of cancer immunotherapy. More recently, advances in the understanding of basic immunobiology (eg isolation and characterisation of dendritic cells, the critical antigen-presenting cell, APC), combined with preliminary but compelling cell-based tumour vaccine human data have created renewed interest in a variety of cellular immunotherapies to treat cancer.

The shared goal of these cell-based approaches is the induction of non-toxic, specific, cellular immune (ie cytotoxic T lymphocyte, CTL) responses in order to break tumour tolerance. CTLs are activated and proliferate in response to specific protein fragments (peptides) presented in the context of cell membrane-spanning proteins which are recognised by circulating T lymphocytes, some of which are CTLs. Evasion of this directed CTL immune response by tumours occurs because of a complex array of tumour-specific and host factors. Manipulating this interplay to enhance the tumour-specific CTL immune response is of fundamental importance to the success of these endeavours.

Though significant scientific progress in this field has been made in recent years, several critical issues require further investigation. Among these are:

- identification of immunogenic tumour-specific antigens across cancer types;
- optimisation of native tumour antigens in order to enhance the CTL immune response;
- identification of the best mechanism of antigen delivery to the APC;
- optimisation of the mechanism(s) by which CTLs recognise tumour-specific antigens and are activated and proliferate in response to these antigens;
- understanding and enhancement of CTL tumour cell recognition;
- understanding and manipulation of tumour cell evasion mechanisms.

Despite these unresolved matters, clinical progress is being made by investigators approaching this field along several fronts. Broadly, efforts in cell-based tumour vaccine approaches have been two-fold: (1) administering autologous or allogeneic tumour cells that have been manipulated *ex vivo* in various ways in attempts to induce a specific CTL immune response, or (2) expanding dendritic cell populations *ex vivo* followed by alteration of this expanded cell population to present specific tumour antigens upon reintroduction to the patient.

Each of these approaches comes with its own set of advantages and particular challenges. A third cellular vaccine approach, consisting of the *ex vivo* fusion of tumour cells and dendritic cells (DCs) followed by readministration of the fused hybridoma as a vaccine, highlights several of the issues raised by the first two cell-based tumour vaccine approaches, and thus will serve as a general model for the remainder of this discussion.[16]

The underlying assumptions behind tumour cell/DC hybridomas as cancer vaccines are that the antigenic repertoire of tumours is not fully known, and the ability of a tumour to present antigens appropriately may be compromised. Thus, by fusing the primary APC of the immune system with a patient's own tumour, cancer antigens can be processed and presented to the immune system in the appropriate context, leading to the induction of a tumour-specific CTL response as discussed previously. Several academic groups in Europe and the USA independently have developed slightly different methods for creating tumour/APC fusions.[17–19] Two of these groups, one each in Europe and the United States, have focused more specifically on the dendritic cell as the source of APC and have proceeded with early clinical trials in cancer patients with this approach. Preliminary data by German investigators published in *Nature Medicine*[17] in March 2000 reported demonstrable tumour responses in 6 of 17 patients (35 per cent) with advanced renal cell carcinoma vaccinated with tumour/DC hybridomas. Toxicities were negligible.

Ongoing clinical trials utilising the German fusion method have expanded to include patients with advanced breast cancer and melanoma. Confirmatory trials, one of which has compared this vaccination strategy to a more 'standard' biochemotherapy regimen in patients with advanced renal cell carcinoma, have either been completed or are soon to be underway in Germany and at other European sites. Likewise, clinical investigators at the Beth Israel Deaconess Medical Center in Boston, USA, are engaged in clinical trials utilising a fusion vaccine method developed by Dr Donald Kufe at the Dana-Farber Cancer Institute. These trials are focused in patients with advanced breast cancer, melanoma and renal cell carcinoma. Duplication of the German data with larger patient numbers and at multiple academic centres will be a crucial first step in confirming this clinical advance in the development of effective cancer vaccines.

With these new cell-based vaccine therapies come many unanswered questions and novel considerations, which must be considered as regulations for these products are contemplated. First, it needs to be appreciated that thus far toxicities have been minimal. If this continues to be the case, comparative studies to 'standard' treatment approach(es), which are virtually without exclusion associated with significant potential toxicities, will need to be designed to highlight this fact, and interpretation of clinical results in the context of the risk/benefit of these novel vaccine treatments will need to bear this in mind. Second, regulatory authorities should recognise that the 'active ingredient' of these types of cancer vaccine can be difficult to characterise. For example, though preclinical data support the hypothesis that the tumour cell/DC hybridoma is critical to the composition of the fusion vaccine, it should be clearly stated that the entire tumour-derived cell/dendritic cell fusion amalgam is administered as a vaccine.

Thus, owing to the limitations of tumour processing, non-tumour cell types such as endothelial cells and stromal cells are included in the fusion process. Tumour/tumour, DC/DC, DC/non-tumour fusions invariably occur with some frequency. In addition, cell death is a recognised sequela of the fusion process itself. The role these added components play in the overall efficacy of the fusion vaccine remains ill-defined. Furthermore, given that the specific tumour antigens that are responsible for eliciting the desired CTL immune response are not known with this vaccine approach, clinical assessment of the immune response to the vaccine is limited. Thus, until further research both to define the specificity of the

response and/or to develop immunological assays to measure the response are in place, using immune response as an end-point in clinical trial design will be problematic. Third, given that the fusion hybridomas are administered as vaccines intended to elicit an immune response and not to function as viable cells (in fact the fusion vaccine is irradiated prior to administration to the patient), regulations applicable to other cellular products in which cell viability is an important factor may not be relevant. Finally, whether a vaccine contains allogeneic (versus solely autologous) material should be reflected in the consideration of product testing and characterisation. Regulations that govern the administration of allogeneic cell products in the area of transplantation may be relevant for consideration, though not directly transferable, as the expected function of the allogeneic material in this setting is dramatically different.

With potential clinical promise of a novel oncologic therapeutic strategy comes new challenges. As the field of cell-based cancer immunotherapy moves closer to a reality, new guidelines and regulations need to be developed that ensure the safe administration of these treatments without implementing onerous requirements which could stifle the development and commercialisation of these potentially less toxic, more effective, and targeted cancer treatments.

Stem cell therapies for neurodegenerative diseases

Stem cell-based therapies may provide hope for treating several neurodegenerative diseases and conditions. Small molecule and protein therapies have historically failed to treat neurological disorders because of the brain's multiple physical barriers and complex biology. Stem cells, however, exhibit unique characteristics that are critical to treating these neurological diseases such as the ability to regenerate tissue, rejoin neural connections, secrete proteins, adapt to their environment, grow after injection, migrate throughout the brain and/or produce needed neurotransmitters. For these reasons, stem cells are being investigated for an equally long list of diseases such as Parkinson's disease, multiple sclerosis, Huntington's disease, Alzheimer's disease, cancer of the central nervous system, spinal cord injury, retinal degenerative disorders, stroke and trauma to name a few.

It is important to note that 'stem cells' as mentioned in the media and in scientific papers often refer not only to many stem cell lines, but also to cells with stem cell-like characteristics. Classic stem cells have innate abilities to proliferate (self-multiply) and differentiate (become more specific cellular lineages). But cells are also engineered, often by genetic manipulation, to exhibit these stem cell characteristics. This section will refer to both groups under the term 'stem cells'. Further confusing accurate classification, stem cells can be harvested from a number of sources. Stem cells are most often derived from human embryos or adults, animal embryos or adults and from different tissue origins such as the brain, bone marrow, muscle, skin and blood. Thus, there may be only one certainty in the future of stem cell therapy – that no single cell type will be effective for all diseases.

As many neurodegenerative diseases have vastly different aetiologies, diseases will require therapies with equally disparate characteristics. Many believe that Parkinson's disease symptoms can be reversed with the transplantation of dopamine-producing neurons to a focused area of the brain.[20] Others believe that the replaced neurons also need to establish specific neural connections within the striatum and require a cocktail of support astrocytes.[21] No matter which disease mechanism is critical, an effective cellular therapy must remain in the implanted region, engraft in the area, produce dopamine and stay in a differentiated state. Leading cellular candidates with these characteristics include cells derived from fetal porcine tissue (see section on 'Xenografts' above) and human embryonic tissue. It is recognised that the debate about

the ethical issues surrounding the many potential applications of these types of cells in human therapy has only just begun in society.

Cancers of the brain often grow uncontrollably and disperse to numerous areas in the brain, therefore requiring a therapy with a much different profile. Instead of a replacement of neurotransmitters and neural connections, a treatment for glioma needs selectively to destroy the cancerous cells in all regions of the brain while leaving other neural tissue unharmed. Some cells have demonstrated success in preclinical models of brain cancer. For example, genetically altered cells have shown great capacities to migrate throughout the brain, recognise and apoptose glioma cells.[22] The hurdle for these cells will be to eradicate all of the target cell types without introducing a new disease phenotype to the patient such as a newly induced cancer.

Injury states such as stroke, traumatic brain injury and spinal cord trauma require a reconnection of neural structures into or through an injured area. Experiments in animal models have shown that some cell types are able to project axons substantial distances through injured spinal columns while other cell types can establish appropriate neural connections in injured areas.[23–25]

Cells of different origins and lineages will have specific drawbacks as well. Critics suggest tumour-derived cell lines could become malignant after implantation, thereby transferring a new cancer to a patient. Cells derived from tumours have nevertheless been shown to be safe in hundreds of animal tests and a Phase I clinical trial.[26] Other researchers have had great difficulty controlling the differentiation or proliferation of genetically altered cells or embryonic stem cells *in vivo*. Often, once these cells are implanted, they become multiple types of tissue: in the worst possible cases, skin, cartilage or bone could grow accidentally within the neural system. Control of cellular products will be an essential feature. One way to achieve this may be to differentiate and purify genetically altered and embryonic cells extensively in culture before transferring them to a patient. Many people have voiced concerns that xeno-sourced cells might transfer non-human diseases across species as discussed above. Human cells from embryonic sources have a different type of drawback – they carry ethical and moral concerns over their harvest. Adult-derived stem cells are feared to have stem cell concentrations too low to be beneficial. As of yet, there are no methods to identify or select a single stem cell within an adult stem cell culture and thus definitively purify and grow a stem cell culture from a single cell.

No stem cell line has yet emerged as a safe, effective therapy for a neurodegenerative disease. The most recent clinical trials using stem cells for these indications have further demonstrated the safety of cellular implants but resulted in varied efficacy. Certainly, larger, more extensive clinical data will elucidate the efficacy of different cell types as well as the aetiology of neurodegenerative diseases. Moreover, the advantages and limitations of different cell types described here will certainly change as additional human data are compiled. New discoveries in stem cell selective differentiation will add new, potentially therapeutic, cell lines and new discoveries in stem cell proliferation will increase the list of clinical candidates. As one of the first organisations needing to react to this emerging field, regulatory authorities may need to be flexible and ready to establish and enforce new guidelines specific to stem cells in order to speed the approval of effective neurodegenerative treatments and to ensure and maintain product safety.

General regulatory issues

In Europe, the CPMP Draft Points to consider on somatic cell therapy[8] suggest that human tissue-based products with therapeutic benefit should be classified as medicinal products. Industry is therefore left with difficult choices. Does one follow a purely 'Medical Device' stance, where the products restorative and replacement

indications are championed,[27] or a 'Medicines' line, as advocated by this CPMP document, encompassing all of the technical and administrative implications of therapeutic benefit? As with all products, including medical devices, risks must be balanced by benefits, and this should be reflected in the applicable regulations. In this context, it would seem that a range of tissue products does not warrant a blanket 'high-risk' label. For example, autologous tissue-based products have far different risks and requirements from those originating from allogeneic tissue. Also, application of certain allogeneic tissue (such as cartilage or bone) will pose significantly less risk than tissue derived from the central nervous system.

An additional regulatory point of relevance is the unique aspect of cell and tissue therapies that, unlike traditional medicinal products, are often being produced by non-commercial organisations such as hospital laboratories, tissue banks or burn centres. These groups have not been subject to regulatory oversight and often are not familiar with or do not employ the same level of controls as their commercial counterparts. They are usually unfamiliar with raw material testing, in-process controls, final product testing, validation of test methods or process validation procedures. In the interest of protecting the public health, all manufacturers, whether commercial or not, should reasonably be held to the same standards to ensure that cell and tissue products are safe for their intended use in human patients.

Complicating this whole equation in Europe are the products that have been marketed and sold for a number of years in the current pan-European 'regulatory vacuum', and are now supported by their existing clinical uses. Evidence of the efficacy of these products is being accumulated, not necessarily through controlled, randomised clinical trials, but through actual use in patients.

Responsible companies pursue a course, allowing for sufficient development data to be generated, that will ensure public safety and health, while also looking at the ethical issues at stake. Furthermore, these companies clearly respect the need for regulation in this area, and make every reasonable attempt to discuss issues with the relevant regulatory authorities. Presently, without legislation, there is the potential for less responsible players to abuse the regulatory vacuum. Clearly, both the European Medicinal Product (65/65/EEC *et al*.) and the Medical Device (93/42/EEC) legislation only partially cover (the extent depending on the product in question) the technical requirements of quality, safety and efficacy for these products.

Outside the USA and Europe, Japan has recently been developing and implementing a regulatory framework for cell therapies and has encouraged research in this field. We would recommend and welcome a global initiative to harmonise the approaches to regulate tissue- and cell-based therapies using an appropriate forum such as the ICH (International Conference on Harmonisation) process. In addition, it would seem self-explanatory that future regulation would need to be 'multi-disciplinary' in that expertise from both medical device and pharmaceutical/biological regulators will be necessary. This approach is already being taken in the USA, with close interactions between the devices (CDRH), pharmaceutical (CDER) and biologicals (CBER) branches of the FDA.

Conclusions

Products that are manufactured from or composed of human tissue have many unique features, which have to be considered over and above those typically covered by traditional medicinal product or medical device regulation. Regulatory authorities have a responsibility to ensure that future regulation is proportionate to the products, while ensuring safety to citizens and taking ethical considerations, as well as issues potentially related to ownership and confidentiality, into account. Authorities then need to ensure appropriate application of such regulations.

It is clear from the US experience, where the system is still evolving, that a transparent and consistent approach to regulatory oversight sets the stage for development of new fields, such as cell therapies, and helps create an environment where research thrives. Worldwide harmonisation of regulations is particularly important where potential safety issues, such as the transmission of infectious agents, have no national or international borders. In addition, in today's environment, companies need to operate on a global basis, and all players should be subject to the same regulations for the safety of the patients being treated. Even within countries where a well-developed regulatory pathway for cellular therapies exist, there is often inconsistent application of regulation. With no consistent approach to the regulation of these products across the world, this is a barrier to the development and commercialisation of cell- and tissue-based products and this ultimately means that many patients will miss out on these potential new therapies. This by itself is becoming an ethical issue.

Harmonised regulations for tissue engineered products would also provide a basis for regulating the next generation of cell and tissue products, as well as for xenografts and stem cell-based therapies. Product development is generating a body of clinical and scientific evidence to support its potential at a rate that is running faster than regulations can be drawn up to cover them. Industry therefore has an important role in working with the regulatory authorities to ensure that new developments are covered appropriately. Industry is advocating the generation of new, specific legislation to regulate the increasing number of products being developed in this area, and applauds current ICH and other international attempts at global harmonisation. It also recognises that potential ethical issues, related to the application of new technologies, need to continue to be discussed and resolved within society in an open and transparent way.

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