Cellular therapies for spinal cord injury: What will the FDA need to approve moving from the laboratory to the human?

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Abstract—The transplantation of living cells and tissues to restore function and/or provide therapeutic molecules has been an active and ongoing area of research interest for over 25 years. Several of these potential therapies have reached initial clinical trials, and it is likely that applications will continue to expand, and that novel and improved approaches will be explored over the next several years. In the past, many of these experimental approaches were tested in early clinical trials without the oversight of regulatory agencies such as the Food and Drug Administration. However, as novel cellular therapies move from preclinical laboratory findings to the clinical arena, researchers and regulators face new and continually evolving issues and uncertainties involving long-term safety and efficacy. Using adrenal medullary transplantation in the spinal cord for pain as an example, this review presents an overview of past and current regulatory guidelines for moving these promising, novel cellular transplantation therapies from the laboratory to the human.

Key words: cell transplantation, Center for Biologics Evaluation and Research (CBER), chromaffin cells, Food and Drug Administration (FDA), pain, spinal cord injury, regulatory agencies.

INTRODUCTION

As novel cellular therapies move from preclinical laboratory findings to the clinical arena, researchers and regulators face new and continually evolving issues and uncertainties involving long-term safety and efficacy.

The transplantation of whole organs has been in clinical practice for years, but with the exception of bone marrow

and blood for restoration of the hematopoietic system, therapeutic cellular transplantation is still in its infancy. In recent years, novel approaches in the potential restoration of function through cellular transplantation have emerged, including the use of fetal human or xenogeneic neural tissue for Parkinson's disease, ectopically implanted islets for diabetes, Schwann cells and olfactory ensheathing glia for spinal cord injury, encapsulated chromaffin cells for pain, and stem cells for the treatment of diabetes, cardiac disease, and central nervous system (CNS) injuries or diseases. Each of these approaches raises new and perhaps unforeseen challenges that can only be fully appreciated and addressed with experience and the advancement of the field. Since these potential therapies have tremendous potential to improve the clinical outcomes and quality of life for patients suffering from these otherwise mostly incurable conditions, it is critical to provide a rational means to encourage the advancement of research and clinical testing in this area. Thus, a goal of regulatory agencies is to establish guidelines and rules to assure an acceptable and reasonable level of safety, while allowing the exploration of novel cellular therapies to proceed. This article presents a brief overview of current Food and Drug Administration (FDA) guidelines relevant to moving cellular transplantation therapies to clinical trials. Because I have been involved in this research area for a number of years, my previous preclinical and clinical experiences are used as examples here. However, as this is a rapidly evolving field, both for researchers and regulators, it is essential that each potential new cellular therapy be considered individually and that researchers maintain frequent and personal contact with the FDA.

ADRENAL MEDULLARY TRANSPLANTS FOR PAIN: PREVIOUS CLINICAL EXPERIENCES

Transplantation into the CNS, including the spinal cord, can be envisioned for a number of purposes: (1) replacing cellular populations lost following injury, such as motor neurons or inhibitory interneurons; (2) bridging across damaged areas to reestablish interneuronal communication; and (3) providing therapeutic molecules, such as neurotransmitters or neurotrophic factors, via a cellular "minipump" function. The majority of experiences in our laboratory has been with the last approach; thus this review focuses primarily on the use of cellular

transplantation as therapeutic minipumps. The implantation of cells at central or peripheral sites offers a potential means of providing sustained local delivery of active agents for therapeutic targets. Potential benefits of this approach compared with more traditional pharmacologic approaches are several: (1) Therapeutic agents can be delivered long-term, avoiding the need for repeated exogenous administration (such as catheter refilling), since living cells provide a continually renewable supply. (2) Therapeutic agents with biological half-lives too short to be delivered by any other means, such as labile neuropeptides, potentially can be used. (3) Biologically active agents can be delivered at focal sites, such as regions in the CNS, avoiding complications associated with systemic delivery. (4) Cells can be genetically manipulated to deliver a therapeutic "cocktail" of multiple desired agents for different indications. Of course, along with the numerous benefits, there are some drawbacks and limitations: (1) Because cellular delivery is a biological process, it is limited to agents that can be manufactured and secreted by cells (i.e., naturally derived agents). (2) There may also be limits to the achievable levels of a given agent that can be delivered by the cells. (3) Since cells produce a multitude of substances in addition to those of therapeutic interest, many of which cannot be completely defined, the complexity of safety studies is increased in order to ensure that cells do not release potentially detrimental agents when implanted in the host. (4) The success of cell-based therapy is dependent on the survival of implanted cells, which may be limited by immunologic factors, nutrient and oxygen supply, etc. These issues, particularly those surrounding the unknowns of transplanting less than completely characterized cell preparations into a patient, are the basis of many of the concerns of regulatory agencies.

The spinal subarachnoid space is a site particularly amenable to cellular implantation for the delivery of therapeutic neuroactive agents. The use of this approach to manage pain has been explored in several laboratories. Most of this work has focused on the transplantation of adrenal medullary chromaffin cells in the spinal subarachnoid space, as these cells produce numerous agents with analgesic or antinociceptive activity, including opioid peptides, catecholamines, and endogenous N-methyl-D-aspartate (NMDA) antagonists. Adrenal medullary tissue or isolated chromaffin cell transplants have shown efficacy in various preclinical pain models, including the formalin test [1–5], chronic inflammation

[6–8], neuropathic pain models [9–14], central pain models [15–18], and wind-up [19]. Our laboratory at the University of Illinois at Chicago (UIC) published the first papers on the use of this approach in preclinical acute rodent pain models in 1986 [20–21]. Several more UIC papers, including two on chronic arthritic and neuropathic pain models [6,11], and others from other laboratories [4,11], appeared over the next few years, during the late 1980s and early 1990s. Armed with this preclinical data, our group at UIC applied for and successfully obtained internal institutional review board (IRB) approval to conduct a limited clinical trial of five patients with terminal cancer pain in 1991. At that time, FDA approval for this study was not required to proceed.

Approval was obtained from the UIC IRB to enroll 5 patients suffering from intractable pain secondary to nonresectable cancerous lesions with prognoses of 6 months or less. Consenting patients enrolled in the program were administered Cyclosporine A (from Sandoz Pharma Ltd., Basel, Switzerland) the day before the implantation and were instructed to continue this for the first 2 weeks following implantation (10 mg/kg/day). Human donor adrenal medullary tissue was obtained from the Regional Organ Bank of Illinois; donors were adults ranging from 20 to 53 years of age. Routine donor screening for infectious diseases was conducted by the Regional Organ Bank. Adrenal glands were transported in sterile buffer and adrenal medullary tissue was dissected into 1.0 to 2.0 mm^3 pieces and placed in explant culture for 3 to 7 days in the UIC laboratory. Tissue viability was determined by catecholamine release assays and tyrosine hydroxylase immunocytochemistry. On the day of the implantation, an intravenous infusion was started, along with a course of prophylactic antibiotics. Tissue was implanted via lumbar puncture with a 14 ga Touhy needle. A total of 1.5 to 2.0 ml of adrenal medullary tissue (from two adrenal glands) was implanted in each patient. The patients received intravenous fluids following the procedure and were discharged from the hospital without event the following day. Patients and their families used preprinted pain evaluation forms to record pain scores (on a visual analog scale (VAS)) and analgesic consumption. Results were promising overall, and no significant adverse events were noted. Of the original 5 patients, 4 reported improved pain scores and a reduced need for exogenous analgesic agents. Three of these 4 reported stable pain relief for the remainder of their disease duration (nearly 1 year in 2

patients). The results of this clinical trial were published in 1993, and a more complete description can be found in Winnie et al. [22].

A similar protocol was conducted in Toulouse, France, by Lazorthes et al. [23]; the study began in 1995 and continued through 1999. This study was a longitudinal survey that included 15 patients with cancer pain for whom systemic opioids had failed, due to the persistence of undesirable side effects. Consenting patients enrolled in the study had received inadequate pain control from oral morphine and were thus receiving opioids via implanted intrathecal pumps to maintain sufficient pain control before the adrenal medullary implantation. The main evaluation criterion of analgesic activity following the transplantation of human adrenal medullary tissue into the spinal subarachnoid space was the patient's need for intrathecal morphine necessary to control pain. Twelve of the 15 patients reported cessation (5 patients), reduction (2 patients), or stabilization (5 patients) of intrathecal morphine requirements, compared with the continual escalation normally observed during the progression of cancer. Complications were mainly related to side effects of the immunoprotection by oral dosing with Cyclosporine A. Two patients had minor and transient digestive disorders (nausea and vomiting), controlled by a reduction in the prescription; while 2 other patients presented more severe side effects (asthenia, arterial hypertension, increase in creatinin), requiring cessation of Cyclosporine A. Cerebrospinal fluid (CSF) samples in the majority of patients contained increased lymphocyte levels at day 7 postimplantation, which persisted throughout the followup in 4 of the patients (although this did not appear to alter graft viability or activity). When obtainable, autopsy evaluations revealed graft adherence to spinal roots and good graft viability. A more complete description of this study can be found in Lazorthes et al. [24]. A phase II, placebo-controlled trial is currently under way by this group.

Because of the limited availability of human donor tissue, alternative sources and/or the generation of expandable cell lines have been explored. Xenogeneic sources are a possibility, but involve an additional set of considerations associated with potential immunologic issues, as well as zoonoses. One approach in xenotransplantation that has been used in clinical trials is the use of semipermeable polymer membranes to encapsulate xenogeneic cells and limit contact with the host immune system. These membranes theoretically can allow diffusion

of neuroactive substances from the cellular implants and nutrient and trophic support from the host, while providing an immunologic barrier to lymphocytes and antibodies. Other advantages of this approach include the possibility of implant retrieval and the potential use of dividing cell lines. Encapsulation of bovine chromaffin cells in preclinical studies and preliminary clinical trials for cancer pain has been reported [9, 25–29]. For clinical trials, adrenal glands were isolated in a sterile surgical suite from young calves. Bovine chromaffin cells were suspended in alginate matrix and loaded into polyacrylonitrile-polyvinylchloride (PAN/PVC) double-skinned membranes with a molecular weight cutoff of approximately 50,000 d. Following loading, membranes were sealed by a methacrylate resin, and the alginate cross-linked in calcium chloride. For clinical devices, a titanium connector, which was in turn attached to a silicon tether connected to the proximal end, was used for device retrieval. Isolated cells were extensively tested for viability, pathogens, catecholamine output, etc., before they were released for implantation. From 1995 to 1997, CytoTherapeutics, Inc., sponsored a phase I trial in terminal cancer patients, and later a retrievability trial in patients with neuropathic pain. Because this approach had the additional complications of both xenogeneic cells and cells combined with a device, and the trials took place as regulatory agencies were becoming more involved in overseeing cellular transplantation, the company was required to obtain FDA approval. Preclinical safety and toxicity studies were done in sheep, lot release specifications and sterility testing were established, and cells and devices were prepared under good manufacturing practices in a dedicated facility. Enrolled in the study were advanced cancer patients (life expectancies under 5 months) with chronic pain inadequately relieved by conventional therapies. The phase I study included 15 patients who received devices containing 1×10^6 cells, and an extension of 4 patients who received devices containing 3×10^6 cells. Patients were carefully monitored for adverse experiences, vital signs, hematologic and clinical chemistry parameters, immunologic responses, and CSF biochemistry and bacteriology. Pain was rated by VAS and the McGill Pain Questionnaire (MPQ), and medication use recorded. Devices remained in place until death. Of the 15 patients implanted in the first group, devices were in place an average of 96 days (23–220 days). In general, the overall adverse experience profile was consistent with the patient's disease and related complications. Adverse experiences thought to be related to the implant were few and mild, primarily including some postlumbar puncture headaches (2 patients), subcutaneous fluid collections at the implant site (2 patients), and subarachnoid-cutaneous fistula (1 patient), all of which are similar to complications encountered with intrathecal drug administration systems. Most of these resolved spontaneously or after an epidural blood patch. Minimal immunologic consequences were noted. Evidence of analgesic efficacy was indicated by reductions in VAS and MPQ scores in 9 patients, and opiate reduction in 8 of the original 15 patients [27]. A more detailed description of this study can be found in Sagen et al. [30]. This study was followed by a phase II trial conducted at European centers, but findings reportedly did not reach significant clinical efficacy, possibly due to the relatively low numbers of cells that can be accommodated by the capsules.* This approach has not been pursued further.

FDA CONSIDERATIONS

A potential application for adrenal medullary transplantation is to manage spinal cord injury pain. Interestingly, in all three spinal cord injury pain models tested thus far, transplants of adrenal medullary chromaffin cells in the spinal subarachnoid space near the injury site consistently attenuate chronic central pain symptoms to some degree [15–18]. Since this is generally a nonterminal population, long-term safety considerations are of utmost importance. Similar considerations may also apply to other potential cellular transplantation approaches in the treatment of spinal cord injury, such as Schwann cell bridges or stem cell grafts.

The overall FDA approval process for cellular transplants is similar to that for new drugs, and includes preclinical testing, research and development, safety review for an investigational new drug (IND) to commence a phase I trial (to assess mainly safety), and completion of phases II (partly to assess short-term safety, but mainly to assess effectiveness) and III (to assess safety, dosage, and effectivness), leading to submission of a Biologics License Application (BLA, similar to a New Drug Application (NDA)). The FDA is organized into eight offices and

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*Unpublished findings, Astra AB, Sweden.

program centers, including the Office of Regulatory Affairs (ORA), the Center for Food Safety and Applied Nutrition (CFSAN), the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), the Center for Veterinary Medicine (CVM), and the National Center for Toxicological Research (NCTR). The branch most relevant for cellular transplantation studies is CBER, which regulates biologics (although there may be some overlap with CDRH or CDER, depending on the individual applications).

CBER regulates biological products. Current authority for this responsibility resides in Section 351 of the Public Health Service (PHS) Act and in specific sections of the Food, Drug, and Cosmetic Act. CBER is committed to advancing the public health through innovative regulations that ensure the safety, effectiveness, and timely delivery to patients of biological products. The mission of CBER is to protect and enhance the public health through the regulation of biological and related products, including blood, vaccines, tissue, allergenics, and biological therapeutics (http://www.fda.gov/cber/index.html). CBER is responsible for ensuring (1) the safety of this nation's entire blood supply and the products derived from it; (2) the production and approval of safe and effective childhood vaccines, including any future Acquired Immune Deficiency Syndrome (AIDS) vaccines; (3) the proper oversight of human tissue for transplantation; (4) an adequate and safe supply of allergenic materials and antitoxins; (5) the safety and efficacy of biological therapeutics, including an exciting new array of biotechnology-derived products used to treat diseases such as cancer and AIDS.

According to CBER's definition:

Biological products or biologics, in contrast to drugs that are chemically synthesized, are derived from living sources. They can be derived from human, plant, animal, or microorganism sources. Examples of biological products include blood, blood components and derivatives, tissues, allergenic extracts, vaccines, drugs derived from biotechnology, and certain diagnostic products. Other examples include somatic cell therapy, gene therapy, and xenotransplantation, or the transplantation of animal organs or tissues into humans. Most biologics are complex mixtures that are not easily identified or characterized, and many biologics are manufactured using biotechnology. Biological products often represent the cutting-edge of biomedical research and, in time, may offer the most effective means to treat a variety of medical illnesses and conditions that presently have no other treatments available.

CBER's review of new biological products, and for new indications for already approved products, requires evaluating scientific and clinical data submitted by manufacturers to determine whether the product meets CBER's standards for approval. After a thorough assessment of the data, CBER makes a decision based on the risk-benefit for the intended population and the product's intended use. An important recognition is that,

although medical products are required to be safe, safety does not mean zero risk, since all medical products are associated with some level of risk. A safe biological product is one that has reasonable risks, given the patient's condition, the magnitude of the benefit expected, and the alternatives available. The choice to use a biological product involves balancing the benefits to be gained with the potential risks. CBER is committed to a product approval process that maximizes the benefits and minimizes the risks to patients of the biological product.

In 1997, a new proposed approach for regulating cell- and tissue-based products (*Reinventing the Regulation of Human Tissue*) was published in conjunction with the Vice President's National Performance Review (http://www.fda.gov/cber/tissue/rego.htm and http://www.fda.gov/cber/gdlns/celltissue.txt). These proposed guidelines are currently being implemented in phases. The guidelines address what is viewed as the main issues in the use of human cellular tissue transplantation. They provide a tiered approach to cell and tissue regulation, focusing on three general areas of concern: (1) preventing unwitting use of contaminated tissues with the potential for transmitting infectious diseases, such as AIDS and hepatitis; (2) preventing improper handling or processing that might contaminate or damage tissues (using current good tissue practices); and (3) ensuring that clinical safety and effectiveness is demonstrated for tissues that are highly processed, are used for nonnatural purposes, are combined with nontissue components, or are used for a metabolic purpose.

The general rules establish two main categories of cell- and tissue-based products, based on degree of risk:

those that require prior regulatory approval (IND approval) before studies begin and those that do not. The second category includes normal use of conventional tissues (such as skin, bones, ligaments, veins, corneas, dura mater, heart valves, and reproductive tissues), so it would only be subject to infectious disease controls and good tissue practices, and would not entail agency submissions other than registration, listing, and reporting of adverse events (subject to Section 361 of the PHS Act). The guidelines for this second category are: (1) The agency requires that cells and tissues be handled according to procedures designed to prevent contamination and to preserve tissue function and integrity. (2) The agency recommends, but does not require, that screening and testing procedures be followed when reproductive tissues are used between sexually intimate partners, and when tissues are transplanted back into the person from whom they were obtained. (3) The agency requires that infectious disease screening and testing be done for cells and tissues transplanted from one person to another. (4) No agency submissions (premarket approval) are required for most conventional and reproductive tissues. (5) The agency requires that all tissue processing facilities register with the agency and list their products via a simple electronic system. The first category, considerably more stringent, includes manipulated human cells to treat viral infections, Parkinson's disease, Human Immunodeficiency Virus (HIV) infection, and other diseases and conditions, and blood from placental/umbilical cord and processed structural cells and tissues (subject to Section 351 of the PHS Act). The guidelines for this category are: (1) Cells and tissues that were (a) manipulated extensively such that their biological characteristics or relevant functions are altered, (b) were combined with nontissue components, or (c) are to be used for purposes other than those they normally perform, or for a metabolic purpose, unless minimally manipulated and used for their natural function in close relatives of the person from whom they were obtained, would be subject to more comprehensive regulatory requirements. (2) These are regulated as biologics or devices requiring premarket approval by FDA. This entails obtaining an IND or Investigational Device Exemption (IDE) prior to human testing, and approval by FDA (BLA) prior to marketing. Sponsors of such products would have to provide submissions to the agency documenting their use of processing controls aimed at ensuring clinical safety and effectiveness.

Thus, there are four stipulations that will determine whether a cell or tissue transplant must be included in the more stringent category. In order to determine which category a specific application falls under, one must understand these definitions (taken from http://www.fda.gov/cber/gdlns/celltissue.txt):

1. Minimal versus more-than-minimal manipulation—

Minimal manipulation: when the processing does not alter the original relevant characteristics of the tissue. The relevant characteristics are those relating to the tissue's ability to carry out the function of reconstruction and/or repair. Thus, separation of structural tissue into components whose characteristics relating to reconstruction and/or repair are not altered would be minimal manipulation. Other examples of procedures that would be considered to constitute only minimal manipulation include cutting, grinding, and shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or gamma irradiation; cell separation; lyophilization; cryopreservation; and, freezing.

More than minimal manipulation: when the processing alters the biological characteristics (and thus potentially the function or integrity) of the cells or tissue, or when adequate information does not exist to determine whether the processing will alter the biological characteristics of the cell or tissue. Examples include cell expansion, encapsulation, activation, or genetic modification.

2. Homologous versus nonhomologous function—

Homologous function: when used to replace an analogous structural tissue that has been damaged or otherwise does not function adequately. Examples of homologous uses of structural tissues include bone allograft obtained from long bone but used in a vertebra, skin allograft obtained from the arm but used as a skin graft on the face, pericardium used as a structural covering for the brain, human heart valves, and human dura mater.

Nonhomologous function: when used for a purpose different from that which it fulfills in its native state, or in a location of the body where such structural function does not normally occur. Examples of nonhomologous use of structural tissue include amniotic membrane used for wound healing in the cornea (intended to heal a damaged corneal epithelium, a function not normally performed in utero), or cartilage placed under the submucosal layer of the urinary bladder to change the angle of the ureter and thereby prevent backflow of urine from the bladder into the ureter (the cartilage would be acting as a structural

support, its normal function, but in a location where such structural support does not normally exist).

3. Metabolic function—

Products with a metabolic mode of action usually rely on viable, functioning cells (e.g., pancreatic islet cells, pituitary cells, or stem cells) for function. They therefore are sensitive to perturbations and may not retain normal function after the transplantation process. Failure or improper functioning of such products often can have a broad variety of systemic adverse effects and can be life-threatening (e.g., hematopoietic stem cell replacement after marrow ablation by chemotherapy or pancreatic islet cell therapy for diabetes).

4. Combination products—

For combination products with synthetic or mechanical components, the clinical safety and effectiveness of the overall product must be addressed, as well as the function and compatibility of the synthetic or mechanical components. The agency's principal concerns with the use of these materials are that they function correctly, that they last a predictable and adequate length of time, and that they are compatible with surrounding tissue. Clinical trials would thus be required under IND or IDE, as appropriate (it depends on the primary mode of action of the product).

Since most of the cell- and tissue-based transplants for spinal cord injury applications will likely fall in the more stringent category, an IND application will be required, and conversations with CBER have indicated that this would be the case for human adrenal medullary tissue transplantation in spinal cord injury pain patients. Guidelines for IND applications can be found in the Code of Federal Regulations (CFR), Title 21 (http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200221). In particular, Part 312 (*Investigational New Drug Application*) contains the relevant sections for the IND application itself, and forms can be downloaded from http://forms.psc.gov/forms/FDA/fda.html. Other key sections include Parts 610 (*General Biological Products Standards*), which contains information regarding mycoplasma and sterility testing, 1270 (*Human Tissues Intended for Transplantation*), and 1271 (*Human Cells, Tissues, and Cellular and Tissue-Based Products*), which describe current good tissue practices.

Conversations with the FDA have uncovered particular issues that would need to be addressed concerning cell or tissue procurement and processing to establish a range of acceptable lot-to-lot variability and criteria for rejection of tissues or cells for transplantation. These

issues are summarized in *Guidance for Human Somatic Cell Therapy and Gene Therapy* (March 1998), http://www.fda.gov/cber/gdlns/somgene.pdf.

This guidance defines somatic cell therapy as the administration to humans of autologous, allogeneic, or xenogeneic living cells that have been manipulated or processed ex vivo. Manufacture of products for somatic cell therapy involves the ex vivo propagation, expansion, selection, or pharmacologic treatment of the cells, or other alterations of their biological characteristics. Gene therapy is a medical intervention based on modification of the genetic material of living cells. When cells are modified ex vivo for subsequent administration to humans, this is also a form of somatic cell therapy.

Examples of somatic cell therapies include (1) implantation of cells as an in vivo source of a molecular species, such as an enzyme, cytokine, or coagulation factor; (2) infusion of activated lymphoid cells, such as lymphokine-activated killer cells and tumor-infiltrating lymphocytes; and (3) implantation of manipulated cell populations, such as hepatocytes, myoblasts, or pancreatic islet cells, intended to perform a complex biological function.

Because biological products are often complex mixtures that cannot be completely defined, quality control is necessary for both the manufacturing process and the final product. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of the biological product. For these reasons, the methods and reagents involved in the production process should be defined, as well as the lot-to-lot reproducibility. Also, exploratory phase I trials for somatic cell and gene therapy products, such as those most likely encountered in early clinical trials for spinal cord injury, should be based on data that ensure reasonable safety and rationale. Less data may be submitted to support beginning exploratory trials than may be submitted at later stages of product development, especially in the case of severe or life-threatening diseases.

The guidance lists four main areas of concern and questions:

1. Collection of Cells—includes description of cell types (autologous, allogeneic, or xenogeneic; tissue source; etc.) and donor selection criteria (age, sex, or exclusion criteria), including serological, diagnostic, and clinical history data, the presence or likelihood of infection by HIV-1 or HIV-2, hepatitis B or C viruses, Human T-

Cell Lymphotophic Virus 1 (HTLV-1), and other infectious agents (newer guidances for Creutzfeldt-Jakob Disease (CJD) and variant Creutzfeldt-Jakob Disease (vCJD)). For animal species other than human, the guidance includes a description of origin, relevant genetic traits, husbandry, and the health status of the herd or colony. Additional considerations are needed to reduce possible risk of zoonoses, such as tissue typing, if relevant.

2. Cell Culture Procedures—includes quality control procedures (quality of materials, equipment validation, and monitoring); culture media (validation of serum additives and growth factors, records, sources, and lot numbers of components used in culture media); adventitious agents (periodic testing for contamination to ensure that cells are free from bacteria, yeast, mold, mycoplasma, and adventitious viruses); monitoring of cell identity (a) for drift in properties of cell population, (b) overgrowth by different cell types, (c) acceptable limits for culture composition, and (d) quantitative assays for functional potency; characterization of therapeutic entity (if the intended therapeutic effect is based on a particular molecular species synthesized by the cells, e.g., for catecholamines, provide data to show that an appropriate and biologically active form is present); culture longevity (if applicable), using the stability of key characteristics to define the limits of the culture period.

3. Cell Banking Procedures—for use with some somatic cell therapy products that are made repeatedly from the same cell source, and with packaging or producer cells used to make gene therapy vectors.

4. Materials Used During Manufacturing—includes, for example, antibodies, cytokines, serum, protein A, toxins, antibiotics, and other chemical or solid supports (such as beads) that can affect the safety, purity, and potency of the final therapeutic product. Components should be identified clearly and a qualification program with set specifications established for each component. Limits should be established for the concentrations of all production components that may persist in the final product.

CONCLUSION

This overview provides a basis to begin the process of moving from the laboratory to human clinical trials in cell-based transplantation therapies. However, the importance of ongoing discussion with the FDA as the plans progress cannot be emphasized enough, as each individual application and approach will have distinct considerations, and the expectations of the regulatory agencies are in flux as novel cellular therapeutic strategies are evolving.

For information on ordering current and complete copies of the regulations over which FDA has jurisdiction (21 CFR), and subscribing to the Federal Register, contact the Superintendent of Documents, U.S Government Printing Office, Washington, D.C. 20402, 202-783-3238.

All biological IND submissions must be made in triplicate and should be addressed as follows: Center for Biologics Evaluation and Research, HFM-99, Room 200N, 1401 Rockville Pike, Rockville, MD 20852-1448.

Questions regarding IND submissions may be directed to the CBER Manufacturers Assistance and Technical Training Branch, 800-835-4709 or 301-827-1800.

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