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THE FOOD AND DRUG ADMINISTRATION'S STATUTORY AND REGULATORY AUTHORITY TO REGULATE HUMAN PLURIPOTENT STEM CELLS

I. Executive Summary

The Public Health Service Act ("PHS Act"), 42 U.S.C. § 262 and 264, the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), 21 U.S.C. § 201 *et seq.*, and the Food and Drug Administration's ("FDA's") implementing regulations thereof provide the agency with broad authority to regulate both the research into and the use of human pluripotent stem cells ("stem cells") intended to be used as biological products, drugs or medical devices to prevent, treat, cure or diagnose a disease or condition. 1/ Scientific research not intended to be used to develop any FDA-regulated product is not under the oversight and control of FDA.

As described in detail below, FDA has utilized its existing statutory authority to develop a regulatory framework for cellular and tissue materials that has evolved over time as the development and use of such biological materials for therapeutic purposes has increased. This paper briefly reviews these statutory provisions and FDA's evolving regulatory framework.

1/ The scope of this paper is limited to human pluripotent stem cells. FDA has a similar regulatory structure to regulate animal stem cell products used as animal drugs. 21 U.S.C. § 360b. The United States Department of Agriculture would regulate animal stem cell products used in animal vaccines. 21 U.S.C. § 151.

II. Background on the Science of Human Pluripotent Stem Cells

After an egg is fertilized, it forms a single cell that has the potential to develop into a human being. National Institutes of Health, "Pluripotent Stem Cells: A Primer" (January 15, 1999) ("NIH Primer") at 1-2. Because it can develop into an entire human being, this cell is called a "totipotent" cell. This cell then divides into two identical totipotent cells. After several days, the totipotent cell forms a blastocyst, which consists of an outer layer of cells and an inner cell mass. The "inner cell mass cells can form virtually every type of cell found in the human body" except the placenta and supporting tissues. *Id.* at 2. Because these cells can develop most but not all cells they are called "pluripotent" cells. *Id.* Pluripotent cells go on to specialize into "stem cells", which give rise to cells that have a particular function such as blood stem cells.

Pluripotent stem cells have been developed in two different ways. First, they have been "isolated from the inner cell mass at the blastocyst stage." *Id.* at 3. "These cells were grown in culture and found to divide indefinitely and have the ability to form cells of the three major tissue types--endoderm (which goes on to form the lining of the gut), mesoderm (which gives rise to muscle, bone and blood) and ectoderm (which gives rise to epidermal tissues and the nervous system)." Statement of Harold Varmus, M.D., Director, NIH, before the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies (December 2, 1998) at 1. Second, they have been isolated from fetal tissue.

It is also thought that "somatic cell nuclear transfer (SCNT) may be another way that pluripotent stem cells could be isolated." *Id.* at 4. In SCNT, the nucleus from a somatic cell is extracted and transferred to a reproductive cell (from a different person) whose own nucleus has been removed or inactivated. Insertion of the donor cell into the recipient cell may be accomplished directly by injection or by placing the donor nucleus and recipient cell side by side and applying a small burst of electricity to induce fusion of the two. The electrical burst also initiates cell division of the fused cell, which will result in the formation of a blastocyst, from which stem cells may be isolated.

The medical potential for human pluripotent stem cells is unknown at this time but is thought to be extraordinary. "It is not too unrealistic to say that this research has the potential to revolutionize the practice of medicine and improve the quality and length of life." NIH Primer at 7. In his recent Congressional testimony, Dr. Varmus described three potential applications of pluripotent stem cells, two of which are not regulated by FDA and one of which will be regulated by FDA. First, stem cell research could include basic research such as "the identification of the factors involved in the cellular decision-making process that determines cell specialization." Statement of H. Varmus at 3. Second, "[h]uman pluripotent stem cell research could also dramatically change the way we develop drugs and test them for safety and efficacy. Rather than evaluating safety and efficacy of a candidate drug in an animal model of a human disease, these drugs could be tested against a human cell line that had been

developed to mimic the disease process." *Id.* Neither of these potential applications likely would be directly regulated by FDA.

> Perhaps the most far-reaching potential application of human pluripotent stem cells is the generation of cells and tissue that could be used for transplantation, so-called cell therapies. Pluripotent stem cells stimulated to develop into specialized cells offer the possibility of a renewable source of replacement cells and tissue to treat a myriad of diseases, conditions and disabilities including Parkinson's and Alzheimer's disease, spinal cord injury, stroke, burn, heart disease, diabetes, osteoarthritis and rheumatoid arthritis.

Id. at 3-4. These stem cell products, based on their intended use, would be the subject of FDA's regulation as set forth below.

III. FDA's Statutory and Regulatory Authority to Regulate Human Pluripotent Stem Cells

A. The Cornerstones of FDA Jurisdiction: Product Definition and Interstate Nexus

In order for FDA to assert regulatory authority over stem cell related research and products, they must fall within one of the product categories over which FDA exercises jurisdiction and must move in interstate commerce.

To the extent FDA determines that a particular product falls within the definition of a biological product, a drug, or a medical device, jurisdiction will be asserted. Whether a particular product falls within the definition for any of the FDA-regulated product categories will turn, in part, on the intended use of the product. The manufacturer's objective intent, as evidenced by labeling, promotional, and other

relevant materials for the product have long been regarded as the primary source for establishing a product's intended use and thus its status for purposes of FDA regulation. *See United States v. An Article. . . Sudden Change,* 409 F.2d 734, 739 (2d Cir. 1969). While that approach would seem to grant manufacturers unbridled control over the regulatory status of their products, in fact, courts have recognized FDA's right to look beyond the express claims of manufacturers to consider more subjective indicia of intent, such as the foreseeable and actual use of a product, to prove that its intended use subjects it to agency jurisdiction. *See National Nutritional Foods Ass'n. v. Mathews,* 557 F.2d. 325, 334 (2d Cir. 1977); *Action on Smoking and Health v. Harris*, 655 F.2d 236, 240-41 (D.C. Cir. 1980).

Regardless of whether FDA or the manufacturer is characterizing the intended use of a product for purposes of evaluating FDA jurisdiction, it is clear that FDA regulatory authority will not automatically extend to all scientific research on stem cells. Indeed, to the extent such nonhuman research is preliminary in nature and/or is undertaken without an intent to develop a therapeutic product, stem cell research is not subject to FDA jurisdiction. Thus, for example, the basic research to develop stem cell models to evaluate the safety and efficacy of therapeutic products would not be directly regulated. In contrast, any scientific data generated from such a model and submitted to FDA as part of a marketing application would be reviewed by FDA. It is only when the science regarding stem cell use has progressed to the point that development of a particular therapeutic product and its use in humans is envisioned, that FDA regulatory

authority applies and further research must be conducted in compliance with FDA's requirements.

Even if a product falls within one of the defined categories over which FDA asserts jurisdiction, no statutory authority over the product exists unless it moves in interstate commerce. FDA takes an expansive view of what constitutes interstate commerce in order to assure that their regulatory controls reach as many products and related research as possible. In regard to biological products FDA has been particularly aggressive. For example, in its 1993 policy statement regarding somatic cell therapy products, FDA concluded that

> The interstate commerce nexus needed to require premarket approval under the statutory provisions governing biological products and drugs may be created in various ways in addition to shipment of the finished product by the manufacturer. For example, even if a biological drug product is manufactured entirely with materials that have not crossed State lines, transport of the product into another State by an individual patient creates the interstate commerce nexus. If a component used in the manufacture of the product moves interstate, the interstate commerce prerequisite for the prohibition against drug misbranding is also satisfied even when the finished product stays within the State. Products that do not carry labeling approved in a PLA (or NDA) are misbranded under section 502(f)(1) of the [FD&C] Act. . . . . Moreover, falsely labeling a biological product is prohibited under section 351(b) of the PHS Act without regard to any interstate commerce nexus (42 U.S.C. 262(b)).

58 Fed. Reg. at 53250. In all likelihood, FDA would apply the same logic to all cellular and tissue materials that are used in the prevention, treatment, cure or diagnosis of a disease or condition of human beings.

B. FDA Has Jurisdiction to Regulate Stem Cells Under Section 351 of the PHS Act

Under section 351 of the PHS Act, FDA is authorized to regulate biological products introduced into interstate commerce. 42 U.S.C. § 262(a). The PHS Act defines a "biological product" to mean "a virus, therapeutic serum, toxin, antitoxin, vaccine, *blood, blood component or derivative, allergenic product, or analogous product,* or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), *applicable to the prevention, treatment, or cure of a disease or condition of human beings*." PHS Act § 351(i), 42 U.S.C. § 262(i) (emphasis added). This definition includes stem cell products, which are considered by FDA to be analogous to blood, blood components or derivatives if they are used for the prevention, treatment, or cure of a disease or condition of human beings.

Cellular products that currently are regulated by FDA as biological products include: (1) autologous or allogeneic lymphocytes activated and expanded *ex vivo* (*e.g.*, lymphokine-activated killer cells (LAK), tumor infiltrating lymphocytes (TIL cells), antigen specific clones); (2) encapsulated autologous, allogeneic, or xenogeneic cells or cultured cell lines intended to secrete a bioactive factor or factors (*e.g.*, insulin, growth hormone, a neurotransmitter); (3) autologous or allogeneic somatic cells (*e.g.*, hepatocytes, myocytes, fibroblasts, lymphocytes) that have been genetically modified; (4) cultured cell lines; and (5) autologous or allogeneic bone marrow transplants using expanded or activated bone marrow cells when such products are used for the

prevention, treatment, or cure of a disease or condition of human beings. 58 Fed. Reg. 53248, 53250 (Oct. 14, 1993) ("Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products") (the "Somatic Cell Therapy Policy"). In addition, peripheral and umbilical cord blood stem cells that have been more than minimally processed and are intended to prevent, treat, or cure disease also are regulated as biological products. FDA, "A Proposed Approach to the Regulation of Cellular and Tissue-Based Products" (February 28, 1997).

Biologics license applications ("BLAs") (historically referred to as Establishment License Applications ("ELAs") and Product License Applications ("PLAs")) are issued by FDA upon a showing that the establishment and product meets "standards, designed to insure the continued safety, purity, and potency of such products. . . ." *Id.* at § 351(d); 42 U.S.C. § 262(d). These standards were first adopted in the law in 1902. The Biologics Control Act of 1902, Chap. 1378, 32 Stat. 738 (1902). In the early 1970's, FDA incorporated by regulation the requirement of efficacy into the approval standards for biological products. 21 C.F.R. § 601.25. Data to support licensure of a biological product usually must be developed through nonclinical and clinical research.

While a biological product is under clinical investigation, it must meet FDA's investigational new drug ("IND") requirements set forth in 21 C.F.R. part 312 (21 C.F.R. § 601.2). FDA defines the universe of clinical research subject to the agency's jurisdiction as ". . . all clinical investigations of products that are subject to section

505 . . . of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act. . . ." 21 C.F.R. § 312.2. FDA regulates "pre-clinical research" which it defines as ". . . non-clinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by FDA, including . . . human and animal drugs, . . . (and) biological products . . ." 21 C.F.R. § 58.1. FDA regulates this area of research through the enforcement of Good Laboratory Practices on persons and entities carrying out such nonhuman research. 21 C.F.R. part 58.

FDA's IND regulations require that prior to conducting clinical trials, a company submit an IND application to FDA, setting forth its protocols for the study and the scientific basis for believing the product would be safe and effective for particular use(s) in humans. The study may begin within 30 days following submission of an IND application, unless FDA advises otherwise or requests additional time to review the application. 21 C.F.R. § 312.20. Clinical trials generally are conducted in three phases. Once trials have commenced, FDA may stop the trials by placing a "clinical hold" on them because of concerns about, for example, the safety of the product being tested. 21 C.F.R. § 312.42. In addition, all clinical studies must be approved and conducted under the supervision of the Institutional Review Board ("IRB") responsible for the study 21 C.F.R. part 56. Lastly, all patients involved in such clinical research must be provided with informed consent in full compliance with FDA requirements. 21 C.F.R. part 50.

The key elements of the PHS Act framework have been largely unchanged since its original enactment in 1902. As described in greater detail below, this framework has been able to remain in place because FDA has always retained the flexibility to address regulatory issues created by new technologies. Keeping up with continuing advances in the field of modern biotechnology, FDA issues regulations, guidance documents or policy statements to describe whether and how its current statutory and regulatory authority applies to a new technology. As new technology and therapeutic products develop, FDA has carefully exercised its inherent discretion of how to apply the law to ensure that science can advance while the public health is protected. As will be discussed in detail below, FDA currently is exercising its authority over stem cells under section 351 of the PHS Act. *See*, *infra*, Section V.

C. FDA Has the Statutory Authority to Regulate Stem Cells Under Section 361 of the PHS Act

In addition to having authority under section 351 of the PHS Act to regulate stem cell products meeting the applicable statutory definition, FDA also has authority to regulate stem cell products under section 361 of the PHS Act. Section 361 authorizes the Department of Health and Human Services ("HHS") to "make and enforce such regulations as in [its] judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession." 42 U.S.C. § 264. This provision provides the agency with broad discretion to enact regulations necessary to prevent the spread of communicable diseases.

Section 361 serves, in part, as the basis on which FDA currently regulates human tissue intended for transplantation (*i.e.*, minimally manipulated tissue such as corneal tissue, bones, skin, or tendons). 21 C.F.R. parts 16 and 1270. *See* 62 Fed. Reg. 40429 (July 29, 1997) ("Human Tissue Intended For Transplantation"). Section 361 also has served as the basis under which FDA has regulated the source and use of potable water, milk pasteurization, and the transmission of communicable disease through shellfish, turtles, certain birds, and bristle brushes. *Id.* at 40431. *See State of Louisiana v. Mathews*, 427 F. Supp. 174 (E.D. La. 1977) (FDA regulation issued pursuant to section 361 of PHS Act banning the sale and distribution of small

turtles was permissible as necessary to prevent spread of communicable disease). Section 361 also serves as part of the statutory basis on which FDA has imposed requirements to protect the nation's blood supply. *Id*.

As evidenced by this discussion, section 361 of the PHS Act provides FDA with broad authority to enact regulations necessary to protect the public health by preventing the spread of communicable disease. However, while FDA has utilized this provision to ban certain products in interstate commerce, and to establish infectious disease testing and related processing standards for tissue, it has not been used by FDA to adopt premarket approval requirements, or otherwise regulate biomedical research. Thus, FDA does regulate cellular products, in part, under section 361 of the PHS Act because the transfer of such cellular components could convey communicable diseases such as AIDS, hepatitis, and herpes simplex. Indeed, the agency currently uses this statutory authority in conjunction with its other premarket approval authorities to provide a comprehensive regulatory structure for cellular and tissue products, including stem cells. *See id.*

D. FDA Has the Statutory Authority to Regulate Stem Cell Products as Drugs under Section 505 of the FD&C Act

In addition to having authority to regulate stem cell products as biological products under the PHS Act, FDA also has concluded that it has the authority under section 505 of the FD&C Act, 21 U.S.C. § 355, to regulate as a drug any stem cell product that meets the applicable statutory definition. The FD&C Act defines drugs as

"articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals." Section 201(g) of the FD&C Act, 21 U.S.C. § 321(g). The vast majority of "new drugs" regulated under the FD&C Act are various dosage forms of synthetic chemicals or plant derivatives. In contrast, the majority of biological products licensed under the PHS Act are products derived from human cellular or tissue materials. FDA exercises its discretion, based roughly on the product categories described above, in approving products either as new drugs or biological products. The PHS Act makes it clear that if a biological product is licensed under section 351, it shall not be required to also have approval under the FD&C Act. 42 U.S.C. § 262(j).

FDA approves new drugs for marketing, based upon proof of efficacy and safety, under section 505 of the FD&C Act. 21 U.S.C. § 355. Manufacturers submit their preclinical and clinical data to establish the safety and efficacy of a new drug pursuant to a New Drug Application ("NDA"). During the investigational stage, investigational drugs are regulated under the same authority and in the same manner as investigational biologics. *See, supra,* Section III. B. In order to receive marketing approval, FDA requires properly conducted, adequate and well-controlled studies demonstrating efficacy with sufficient levels of statistical assurance to support product approval. Reports of these clinical trials as well as preclinical data must be submitted along with information pertaining to the preparation of the drug, analytical methods,

drug product formulation, details on the manufacture of finished products and proposed packaging and labeling. 21 C.F.R. § 314.50. Once a drug product is approved it is subject to continuing regulation by FDA such as compliance with Good Manufacturing Practices ("GMPs") and marketing and advertising restrictions. 21 C.F.R. §§ 202, 210, 211. In addition, FDA may require additional clinical tests following approval to confirm safety and efficacy (Phase IV clinical trials).

During the pre- and post-approval periods, drugs and biological products are subject to the adulteration and misbranding provisions of the FD&C Act. 21 U.S.C. §§ 351, 352. Section 501 of the FD&C Act provides in part that a product is adulterated if it is a drug that was not manufactured in conformance with GMPs or was prepared, packed or held under unsanitary conditions. 21 U.S.C. § 351(a). A product is misbranded if, among other things, its labeling is false or misleading in any particular or if any word, statement or other information requested to appear on the label or labeling is not prominently placed thereon. *Id.* at § 352. Also during the pre- and post-approval periods, drug products are subject to FDA's general prohibitions against promoting products for unapproved or "off-label" uses.

In bringing enforcement actions against biological products licensed under the PHS Act, FDA routinely utilizes various provisions of the FD&C Act drug adulteration and misbranding authorities as part of any such action. In addition, FDA utilizes some of the enforcement authorities of the FD&C Act, such as seizures or

injunctions, to enforce both laws against biological products they deem violative. 21 U.S.C. §§ 322; 334.

E. FDA Has the Statutory Authority to Regulate Stem Cell Products as Devices under the FD&C Act

Section 201(h) of the FD&C Act defines a medical device, in pertinent part, as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article which is (1) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (2) intended to affect the structure or any function of the body of man or other animals," and which is not dependent upon being metabolized for the achievement of its primary intended purposes. 21 U.S.C. § 321(h). To the extent FDA concludes that stem cell products meet the definition of a device and operate in a manner similar to human tissue products used for transplantation (*e.g.*, heart valve allografts and human lenticules--corrective lenses derived from human corneal tissue), they may be subject to regulation as devices.

Under section 513 of the FD&C Act, all medical devices are classified into one of three classes -- Class I, Class II, or Class III. 21 U.S.C. § 360(c). A device's class determines the types of regulatory controls it is subject to and the process it goes through to receive marketing approval from FDA. Most medical devices in the United States fall within Classes I or II and are marketed pursuant to a simplified approval process set forth in section 510(k) of the FD&C Act known as

"Premarket Notification" (or "510(k) clearance"). 21 U.S.C. § 360(k). A medical device that does not qualify for 510(k) clearance is placed in Class III, which is reserved for devices classified by the FDA as posing the greatest risk (*e.g.*, life-sustaining, life-supporting, implantable, or devices presenting a potentially unreasonable risk of injury). Stem cell products, to the extent FDA considers them to be devices, would most likely be placed in Class III. A Class III device generally must undergo the premarket approval ("PMA") process, prior to marketing which requires the manufacturer to prove the safety and effectiveness of the device to the FDA's satisfaction. A PMA application must provide extensive preclinical and clinical trial data and also information about the device and its components regarding, among other things, manufacturing, labeling and promotion. 21 C.F.R. § 814.20. As in the case of drugs and biologics, the data standards applied to devices in a PMA submission require the manufacturer to demonstrate that the device is safe and effective under the conditions of use recommended in the labeling. FD&C Act § 515(d); 21 U.S.C. § 360e(d).

A clinical study in support of a PMA application requires an Investigational Device Exemption ("IDE") application approved in advance by the FDA for a limited number of patients . FD&C Act § 520(g); 21 U.S.C § 360j(g) The IDE application must be supported by appropriate data, such as animal and laboratory testing results. 21 C.F.R. part 812. The clinical study may begin if the IDE application is approved by the FDA and the appropriate institutional review board ("IRB") at each

clinical study site. 2/ In all cases, the clinical study must be conducted under the auspices of an IRB pursuant to FDA's regulatory requirements intended for the protection of subjects, including execution of informed consent, and to assure the integrity and validity of the data. 21 C.F.R. part 56.

As with drugs and biologics, devices manufactured or distributed pursuant to FDA clearance or approval are subject to pervasive and continuing regulation by the FDA and certain state agencies. They are also subject to the same rules regarding adulteration and misbranding. *See, supra,* Section III. D.

2/ While it is true that if the device presents a "nonsignificant risk" to the patient, a sponsor may begin the clinical study after obtaining IRB approval without the need for FDA approval, this would not likely apply to stem cell research.

IV. Historical Application of Statutory Authority to Cellular and Tissue Materials

A brief historical review of FDA's application of the statutes described above to cellular and tissue materials shows that FDA has been cautious in exercising its regulatory discretion.

> FDA has never had a single regulatory program for human cellular and tissue-based products. Instead, it has regulated these products on a case-by-case basis responding as it determined appropriate to the particular characteristics of and concerns raised by each type of product.

63 Fed. Reg. 26744 (May 14, 1998) (FDA Proposed Rule "Establishment and Listing for Manufacturers of Human Cellular and Tissue-Based Products"). One example, has been FDA's approach to regulating bone marrow. While for years FDA has licensed blood and blood components pursuant to section 351 of the PHS Act, 42 U.S.C. § 262, FDA has voluntarily refrained from regulating minimally manipulated bone marrow, the earliest source of stem cells used for transplantation, despite its status as a blood component. Indeed, not until the early 1990's did FDA announce that to the extent bone marrow was subject to extensive manipulation prior to transplantation, it would be treated the same as somatic cell therapy and gene therapy products subject to the IND regulations and requiring PHS Act licensure. 58 Fed. Reg. 53248, 53249 (Oct. 14, 1993).

Also in 1993, in response to concerns about the transmission of the human immunodeficiency virus and other infectious diseases, FDA published an

emergency final rule which established certain processing, testing and recordkeeping requirements for certain types of tissue products. "Human Tissue Intended for Transplantation" 58 Fed. Reg. 65514 (Dec. 14, 1993). This rule, however, did not mandate premarket approval or notification for all tissues, but rather provided, among other things, for donor screening, documentation of testing, and FDA inspection of tissue facilities. 3/

As another example of FDA's case-by-case approach, in 1996, FDA published a guidance stating that manipulated autologous structural ("MAS") cells, which are autologous cells manipulated and then returned to the body for structural repair or reconstruction, are subject to PHS licensure. CBER, Guidance on Applications for Products Comprised of Living Autologous Cells Manipulated Ex Vivo and Intended for Structural Repair or Reconstruction (May 1996). Similarly, until very recently FDA carefully chose not to regulate reproductive tissues. Then, as will be discussed below, in 1997, FDA proposed that in the future certain reproductive tissues, such as semen, ova and embryos, should come under some form of regulation.

Traditional tissue products, including but not limited to bone, skin, corneas, and tendons, also have been subject to FDA's piecemeal regulatory approach. Historically, FDA regulated these products on an ad hoc basis as medical

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3/ In 1997, FDA finalized its 1993 emergency rule establishing processing, testing and recordkeeping requirements for all tissue products. "Human Tissue Intended for Transplantation" 62 Fed. Reg. 40429 (July 29, 1997).

devices under section 201 of the FD&C Act. *See, e.g.*, 63 Fed. Reg. 26744 (citing as examples, dura mater, corneal lenticules, and umbilical cord vein grafts). However, with the advent of HIV and the potential for its transmission, FDA concluded in the early 1990's that a more comprehensive program for traditional tissues was necessary. In 1991, FDA concluded that human heart valves were medical devices subject to premarket approval requirements. "Cardiovascular Devices; Effective Date of Requirement for Premarket Approval; Replacement Heart Valve Allograft" 56 Fed. Reg. 29177 (June 26, 1991). After a period of litigation, FDA relented somewhat and concluded that while these products remained medical devices, they would not be subject to premarket approval requirements. FDA Rescission Notice, 59 Fed. Reg. 52078 (October 14, 1994). In defining tissue subject to this rule, FDA exempted a number of products, including vascularized organs, dura mater, allografts and umbilical cord vein grafts. *Id.* at 40434.

This very brief review of the regulatory landscape shows a regulatory framework that, in FDA's own words, has been "fragmented." FDA has regulated most of these products on an ad hoc basis either as medical devices or biological products or, in certain instances, chose not to regulate certain of these products at all. As a result of the agency's own reevaluation and Congressional concerns and pressure in the mid-1990's, FDA concluded that a comprehensive approach to the regulation of these products was an important step forward in public health protection.

V. Comprehensive FDA Policy to Regulate Cellular or Tissue-Based Products, Including Pluripotent Stem Cells

In February 1997, FDA proposed, consistent with the existing statutory framework set forth above, a new approach to the regulation of human cellular and tissue-based products. This framework is intended to "protect the public health without imposing unnecessary government oversight." "Reinventing the Regulation of Human Tissue," National Performance Review (February 1997) at 1.

The 1997 document establishes the further evolution of FDA's application of the PHS Act and FD&C Act to cellular and tissue products. While still a proposed approach, it utilizes FDA's existing statutory authority under the PHS Act and FD&C Act to regulate a broad array of cellular and tissue materials.

The framework proposes a tiered approach to the regulation of cellular and tissue-based products. FDA, "A Proposed Approach to the Regulation of Cellular and Tissue-Based Products" (February 28, 1997) (the "Proposed Approach"). Products that pose increased risks to health or safety would be subject to increased levels of regulation (*i.e.*, either licensure under the PHS Act or premarket approval under the FD&C Act. For example, products that pose little risk of transmitting infectious disease would be subject to minimal regulation (*i.e.*, facility registration and product listing). However, products that are (1) highly processed (more-than-minimally manipulated), (2) are used for other than their normal purpose, (3) are combined with nontissue components (*i.e.,* devices or other therapeutic products) or (4) are used for metabolic

purposes (*i.e.,* systemic, therapeutic purposes) will be required to be clinically investigated under INDs, IDEs and subject to premarket approval as biological products, medical devices or new drugs.

The Proposed Approach addresses FDA's regulation of stem cell products. In the case of a minimally manipulated product for autologous use and allogeneic use of cord blood stem cells by a close blood relative, FDA proposed requiring compliance with standards consistent with section 361 of the PHS Act rather than an IND and licensure pursuant to section 351 of the PHS Act. However, minimally manipulated products that will be used by an unrelated party will be regulated under section 351 of the PHS Act. The agency intends to develop standards, including disease screening requirements, establishment controls, processing controls, and product standards. "If sufficient data are not available to develop processing and product standards after a specified period of time, the stem cell products would be subject to IND and marketing application requirements." Proposed Approach at 25. Stem cell products that are more than minimally manipulated will require INDs and licensing under section 351 of the PHS Act. For example, stem cell products that are used for a non-homologous function or are more than minimally manipulated will be required to be licensed under section 351. FDA has "increased safety and effectiveness concerns for cellular and tissue-based products that are used for non-homologous function, because there is less basis on which to predict the product's behavior." Proposed Approach at 16.

2. FDA Implementation of the Proposed Approach

FDA has begun to implement the Proposed Approach. 4/ On January 20, 1998, FDA published a "Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products." 63 Fed. Reg. 2985 (Jan. 20, 1998) utilizing its standards-setting authority under section 361 of the PHS Act. In this notice, the agency requests product standards to ensure the safety and effectiveness of stem cell products, which should be supported by clinical and nonclinical laboratory data. FDA also announced its intention to phase in after three years implementation of investigational new drug application ("IND") and license application requirements for minimally manipulated unrelated allogeneic hematopoietic stem/progenitor cell products. *Id.* The notice states that "[i]f adequate information can be developed, the agency intends to issue guidance for establishment controls, processing controls, and product standards. . . . FDA intends to propose that, in lieu of individual applications containing clinical data, licensure may be granted for products certified as meeting issued standards." If, however, FDA determines that adequate standards cannot be developed, the agency has expressed its intention to enforce IND and licensing requirements at the end of three years. Proposals are due on or before January 20, 2000.

4/ While FDA may choose to implement this policy through regulation, FDA also may implement it on a case-by-case basis. *See, infra*, Section VI.

On May 14, 1998, FDA proposed "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products." 63 Fed. Reg. 26744 (May 14, 1998). The agency describes the proposed registration and listing requirements as a first step towards accomplishing the agency's goal of putting in place a comprehensive new system of regulation for human cellular and tissue-based products. Registration and listing is intended to allow FDA to assess the state of the cell and tissue industry, "to accrue basic knowledge about the industry that is necessary for its effective regulation", and to facilitate communication between the agency and industry. *Id.* at 26746. As proposed, the registration and listing requirements would apply to human cellular and tissue-based products that FDA will regulate under section 361 of the PHS Act. 5/ Among the products cited by FDA as regulated under that section and consequently subject to registration and listing are bone, tendons, skin, corneas, as well as peripheral and cord blood stem cells under certain conditions and sperm, oocytes, and embryos for reproductive use. *Id.* at 26746.

VI. FDA Has the Legal Discretion to Regulate Stem Cell Products in a Variety of Ways. Moreover, FDA's Discretion is Entitled to Great Deference

Although, as described above, the PHS Act sets forth the basic framework for the regulation of biological products and that law is complemented by

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5/ Consistent with the discussion *supra,* Section III. A, the preamble to the proposed rule states that "use of human cellular or tissue-based products solely for nonclinical scientific or educational purposes does not trigger the registration or listing requirements. Any use for implantation, transplantation, infusion, or transfer into humans is considered clinical use and would be subject to part 1271 [the registration and listing requirements]." *Id.* at 26748.

the FD&C Act, Congress gave FDA significant discretion regarding the manner in which FDA approves and regulates these products. This is entirely appropriate given the rapidly changing nature of biotechnology.

Today there is a vast array of biological products that have been approved by FDA and many others that are awaiting FDA action. 6/ These products are scientifically complex and rarely lend themselves to categorization. As a result, FDA invariably is required to determine on a case-by-case basis whether its existing statutory authority applies to a new product, which particular authority to apply and, if so, what evidence will adequately demonstrate proof of safety, purity, and potency (efficacy). The decision whether and how to regulate a product is made based on FDA's expert determination and is based on the particular facts and circumstances, the historical application of the law to similar products, the applicable statutory and regulatory criteria , and the state of FDA's scientific understanding at the time of the approval.

The decision to leave this determination to FDA's discretion and expertise was a wise policy decision by Congress. The success of the approval process for cellular and tissue products is in many ways dependent upon FDA's appropriate

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6/ Today biological products are available or under development to treat, diagnose, or prevent virtually every serious or life-threatening disease. Available products include, but are not limited to, vaccines (manufactured both in traditional ways and through the use of biotechnology); human blood and blood-derived products; monoclonal or polyclonal immunoglobulin products; human cellular (*i.e.*, gene therapy) products; protein, peptide and carbohydrate products; protein products produced in animal body fluids by genetic alteration of the animal (*i.e.*, transgenic animals); animal venoms; and allergenic products.

application of discretion to respond as it sees fit to any particular product within the basic statutory and regulatory framework discussed above. Otherwise, FDA would be unable to respond to the almost daily developments in biotechnology and the complex scientific issues presented by each particular product. Absent this discretion, the cellular and tissue product approval process would grind to a halt.

When FDA exercises the significant discretion provided to the agency by Congress, FDA's exercise of this discretion is entitled to great deference. *U.S. v. Rutherford*, 442 U.S. 544, 553 (1979); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 216 (D.D.C. 1996). In a recent challenge to FDA's approval of a biological product under the PHS Act, the District Court for the District of Columbia held that "FDA's policies and its interpretation of its own regulations will be paid special deference *because of the breadth of the Congress' delegation of authority to FDA and because of FDA's scientific expertise." Berlex Laboratories, Inc. v. FDA et al.*, 942 F. Supp. 19 (D.D.C. 1996) (emphasis added). *See also Lyng v. Payne*, 476 U.S. 926 (1986).

Moreover, even if FDA has not asserted jurisdiction previously with regard to reproductive tissue, for example, it is appropriate that FDA's policies in this area are evolutionary. The Supreme Court has recognized that expert administrative agency interpretations are not "carved in stone. On the contrary, the agency . . . must consider varying interpretations and the wisdom of its policy *on a continuing basis*." *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 863-64 (1984)

(emphasis added). Furthermore, the Court has acknowledged that "regulatory agencies do not establish rules of conduct to last forever. . . . [A]n agency must be given ample latitude to 'adapt their rules and policies to the demands of changing circumstances.'" *Motor Vehicle Mfrs. Ass'n of the U.S. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42 (1983) (citations omitted).

VII. Conclusion

The extensive statutory and regulatory authority available to FDA will ensure that the agency's regulatory approach can continue to evolve to keep up with the rapidly changing world of biotechnology. Despite the patchwork quilt of regulation applied through the mid-1990's, FDA has now developed a comprehensive regulatory approach to the regulation of cellular and tissue-based therapeutic products under its jurisdiction, including pluripotent stem cells. Nonclinical and clinical stem cell research undertaken to develop a therapeutic product intended to treat human disease will continue to be regulated by FDA while basic scientific research and other nonhuman research will remain outside the agency's purview.