

ARTICLES

HUMAN TISSUES AND REPRODUCTIVE CLONING: NEW TECHNOLOGIES CHALLENGE FDA

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INTRODUCTION

It is conventional wisdom that regulatory agencies possess discretion to interpret their program statutes in new ways in order to meet challenges that the congressional authors did not, and in many cases could not, anticipate. The Supreme Court's famous *Chevron* decision promises, even if it does not guarantee, that reviewing courts will defer to an agency's modernizing initiatives unless it can be shown that Congress specifically foreclosed them.¹ Thus we have come to expect that agencies will often confront new challenges by adapting traditional tools, rather than reflexively returning to the legislature for new authority or instructions. Indeed, agencies often prefer to work within the framework of their original charters, both so as to appear responsive and to avoid the real risk that new legislation will repudiate or undo policies to which they have long been committed.

There must, of course, be limits to administrative interpolation, though it may be futile to attempt to describe them in general terms. *Chevron's* dictate, that when Congress has spoken clearly to the pre-

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¹ *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 844 (1984).

cise issue the Agency, like the Court itself, is bound, provides imperfect guidance. Indeed, the Court's language is often invoked to label a conclusion rather than to guide judicial inquiry.² It is always easier to know when an agency has gone "too far" after a court has nullified a modernizing effort than to predict that result in advance.

The U.S. Food and Drug Administration (FDA) confronts more than its share of novel challenges. The Agency's jurisdiction, spanning a quarter of the consumer market, also encompasses some of the country's most innovative enterprises, enterprises that are exploiting continuing discoveries in the biological sciences to conceive, develop, and market technologies with which regulators have little knowledge or relevant experience. Within the past decade FDA has been confronted with pressures to "deal with" gene therapy, recovery (and future use) of umbilical cord blood, allograft tissue transplants, techniques to assist reproduction, stem cell research, and even human cloning.³ In various ways, with different degrees of urgency, and with varying degrees of confidence that it possesses the needed resources or legal authority, the Agency has responded—often, though not always, successfully. One theme has been constant, however. In none of these instances has FDA acknowledged that it might need help from Congress in the form of new statutory jurisdiction or new administrative tools. It has instead insisted that existing laws both confer jurisdiction and provide the necessary means of control.⁴

² See generally Michael Herz, *Deference Running Riot: Separating Interpretation and Lawmaking under Chevron*, 6 ADMIN. L.J. AM. U. 187 (1992); see also Orin S. Kerr, *Shedding Light on Chevron: An Empirical Study of the Chevron Doctrine in the U.S. Courts of Appeals*, 15 YALE J. ON REG. 1 (1998); Thomas W. Merrill & Kristin E. Hickman, *Chevron's Domain*, 89 GEO. L.J. 833 (2001); Richard J. Pierce Jr., *Chevron and its Aftermath: Judicial Review of Agency Interpretations of Statutory Provisions*, 14 VAND. L. REV. 301 (1988); Peter H. Schuck & E. Donald Elliot, *To the Chevron Station: An Empirical Study of Federal Administrative Law*, 1990 DUKE L.J. 984 (1990); Kenneth W. Starr, *Judicial Review in the Post-Chevron Era*, 3 YALE J. ON REG. 283 (1986); Cass R. Sunstein, *Law and Administration After Chevron*, 90 COLUM. L. REV. 2071 (1990).

³ See Human Tissue Intended for Transplantation, 58 Fed. Reg. 65,514 (Dec. 14, 1993); see also Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, 58 Fed. Reg. 53,248 (Oct. 14, 1993); David A. Suski, *Frozen Blood, Neonates, and FDA: The Regulation of Placental Umbilical Cord Blood*, 84 VA. L. REV. 715, 716 (1998); Philip J. Hilts, *Skin Grown in Lab Offers New Hope for Burns and Unhealable Wounds*, N.Y. TIMES, June 28, 1995, at C10; "Dear Colleague" letter from Stuart L. Nightingale, M.D., Associate Commissioner, Food and Drug Administration (Oct. 26, 1998).

⁴ Proposed Approach to Regulation of Cellular and Tissue-Based Products, 67 Fed. Reg. 9721 (Mar. 4, 1997); Human Tissue Intended for Transplantation, 58 Fed. Reg. 65,514 (Dec. 14, 1993); Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, 58 Fed. Reg. 53,248 (Oct. 14, 1993); Richard A. Mer-

If measured by its avoidance of judicial nullification, FDA's handling of these new technologies has surely been a success. With the exception of its failed attempt to regulate an old technology, tobacco,⁵ FDA has escaped outright judicial rejection of its initiatives. But this success may be attributable to the hesitant steps by which the Agency has proceeded, leaving difficult issues un-addressed, and to the unpredictable pace of private sector innovation which has sometimes meant that threatened regulations have not yet begun to bite. Thus we cannot look to judicial decisions for the answer to the question whether FDA has gone too far or, conversely, whether it has not been empowered to go far enough.

This article continues an ongoing inquiry into the question whether FDA now possesses the tools—the statutory authority, the decisional processes, the relevant expertise—to "deal" responsibly with the challenges that new medical technologies pose, for government and for society. The conclusions offered are tentative, and the analysis is exploratory. Part I describes FDA's basic regulatory weaponry—the tools Congress has given it to regulate products within its jurisdiction. Parts II and III, the centerpiece of the article, chronicle and compare FDA's responses to two innovative medical technologies—human tissue transplants and human cloning. Part IV offers some tentative conclusions about the persistent question, which can be framed in two ways: Has FDA, in legal vernacular, "gone beyond its brief"? Has Congress failed to equip FDA with the instruments needed to regulate biomedical technology in the 21st century?

I. FDA'S EXISTING EQUIPMENT

FDA's regulatory authority derives mainly from the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA)⁶, as repeatedly amended, and its primary instrument for regulating new medical technologies is provided by Section 505 of the Act—the section governing "new drugs."⁷ Experts will know this summary is incomplete because it omits reference to the FDCA provisions that

rill & Gail H. Javitt, *Gene Therapy, Law and FDA Role in Regulation*, in ETHICAL, LEGAL, AND POLICY ISSUES IN BIOTECHNOLOGY 329 (Thomas J. Murray & Maxwell J. Mehlman, eds., 2000) [hereinafter Merrill & Javitt]; "Dear Colleague" letter from Stuart L. Nightingale, M.D., Associate Commissioner, Food and Drug Administration (Oct. 26, 1998).

⁵ Food and Drug Admin. v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 126 (2000).

⁶ 21 U.S.C. § 331 (2002) (listing actions prohibited under FDCA).

⁷ See 21 U.S.C. § 355 (2002).

empower FDA to regulate medical devices and appears to ignore the Public Health Service Act, pursuant to which FDA must approve all biological products.⁸ The first of these qualifications is surely legitimate, and I will in due course address the possibilities afforded by the medical device law. The second is unimportant, because, according to FDA, all biologics are also drugs, and since all biologics require approval, the Agency's basic requirements for ordinary drugs and biological "drugs" are similar.⁹ Furthermore, to regulate developmental activities that precede marketing of biologics—such as preclinical and clinical testing—FDA has relied on the FDCA requirements applicable to "new drugs." Thus, for purposes of assessing the adequacy and flexibility of FDA's existing authorities, the FDCA's requirements for drugs are a sensible place to start.

I have described these requirements in more detail elsewhere.¹⁰ A summary should suffice here.

It is an offense to market a "new drug"—a category that encompasses practically every prescription drug and many over-the-counter drugs—without an FDA-approved New Drug Application (NDA).¹¹ To gain approval of an NDA, the sponsor of the drug (usually the manufacturer) must submit voluminous information to FDA, including information about the active ingredient, the chemistry of the formulation for delivering the active ingredient, methods of manufacture and packaging, proposed labeling, and, most critically, the results of clinical studies that will support a conclusion that the drug product is safe and effective.¹² In sheer volume, the reports of required clinical studies of a drug typically dominate the application, and the interpretation of the results of those studies is usually the most challenging part of the approval process.¹³

⁸ 42 U.S.C. §262 (2000) (originally Biologics Act of 1902); see also PETER HUTT & RICHARD MERRILL, *FOOD AND DRUG LAW* 663-665 (2d ed. 1991) [hereinafter Hutt & Merrill Text].

⁹ Procedures for Review of Safety, Effectiveness, and Labeling, 37 Fed. Reg. 16,679 (Aug. 18, 1972); Human Drugs which are Biological Products: Redefinition of Authority to Administer Certain Provisions of the Federal Food, Drug, and Cosmetic Act, 37 Fed. Reg. 4,004, 4,005 (Feb. 25, 1972).

¹⁰ Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1797-1800 (1996) [hereinafter *Architecture of Government Regulation*].

¹¹ 21 U.S.C. § 355(a) (2002).

¹² 21 U.S.C. § 355(b) (2002).

¹³ See *FDA Approval of Drugs: Hearing Before the House Subcommittee on Oversight and Investigations, House Committee on Commerce*, 104th Cong., 1995 WL 331824 (F.D.C.H.) (May 25, 1995) (statement of Kenneth I. Kaitin, Ph.D., Associate Director, Tufts Center for the Study of Drug Development, Tufts University, Boston, Mass.) (indicating that on average it takes

Prior to approval, FDA has considerable authority over whether and how the drug may be administered to human beings. Once a drug gains FDA approval, however, the Agency's capacity to control how it is marketed and, more important, how it is used by physicians is significantly diminished. FDA will occasionally demand, as a condition of approval, the conduct of additional clinical studies and it will monitor the manufacturer's promotion of the product and/or physicians' use of the product. And it may initiate enforcement action against the manufacturer for failure to comply with labeling requirements or for ignoring limits on promotion, but in this role FDA functions as a police officer, addressing conduct after the fact, rather than as a gatekeeper, empowered to impose restrictions that must be satisfied before the product can be distributed at all.

The statutory requirement that a drug be shown to be safe and effective before it can be distributed would be a "Catch-22" if distribution were—as it almost always is—necessary to permit the clinical studies that are the accepted means of demonstrating safety and effectiveness. The statute resolves this conundrum by allowing FDA to approve limited distribution for the sole purpose of conducting studies in human subjects.¹⁴ The mechanism for such approval is an Investigational New Drug Application or IND. Thus it is FDA's authority to approve, or withhold approval of, an IND that empowers it to oversee clinical investigation of new technologies that fall within the "new drug" definition.

The Agency has established limits on such studies, limits whose observance is a condition for IND approval. The sponsor of any study of an unapproved drug in humans must submit to FDA detailed information about the drug, about the planned course of study, about study protocols, about the identity and location of the investigators in charge of the studies, and about the measures taken to assure the protection of participating subjects—volunteers in the initial stage, patients with the disease or condition to be treated as studies progress.¹⁵ The protection of study subjects is a central objective of the law that permits FDA to approve INDs and of the Agency's own standards and procedures. By statute, FDA is required to insist that any study of an investigational drug have been

8.5 years for approval of a new drug, an average of six of those years are spent in clinical testing, and that increase in review time corresponds to increasing volume of clinical testing).

¹⁴ 21 U.S.C. § 355(i) (2002).

¹⁵ 21 C.F.R. § 312.23 (2002).

reviewed and approved by the human subject protection entity (conventionally titled Institutional Review Board) at the institution or institutions where the studies are to be performed.¹⁶ Thus, it can be said that FDA collaborates with local IRBs in reviewing, approving, and policing pre-marketing human studies of new drugs. For new technologies that it will treat as drugs, the FDCA and its implementing regulations give FDA substantial control over their development, clinical testing, and market introduction.

Two features of the system just sketched are significant in the present context. First, the process for developing, testing, and agency review of new drugs is very expensive. A major reason it is expensive is that it takes a long time. For many years the focus of complaints about delay was the stage at which FDA reviewed the copious materials submitted by drug sponsors in their NDAs.¹⁷ Even greater concern is directed at the length of time required to design and conduct the clinical trials that are now regarded as necessary to establish the safety and effectiveness of new therapies. FDA's own demands account for part of this painstaking process, but the complexity of many innovative technologies and the difficulty of demonstrating that they make genuine contributions to human health are also factors. The cost of clinical studies rises with the time required, the number of study sites, and the size of patient populations. The result is that very substantial expenditures are required to bring a new drug to market through the existing system.¹⁸ Accordingly, innovators and the Agency alike are regularly confronted with the question whether this costly system should or must apply to a particular technology.

The second notable feature of the IND/NDA system is secrecy. From the beginning of the new drug approval system in 1938, which required the sponsor of a new drug to submit the evidence it had assembled (and paid for), FDA took the position that this informa-

¹⁶ 21 C.F.R. § 56 (2002).

¹⁷ See generally William M. Wardell, *A Close Inspection of the "Calm Look": Rhetorical Amblyopia and Selective Amnesia at the Food and Drug Administration*, 239 JAMA 2004 (1978); William Wardell, *The Drug Lag Revisited: Comparison by Therapeutic Area of Patterns of Drugs Marketed in the United States and Great Britain from 1972 Through 1976*, 24 CLINICAL PHARMACOLOGY & THERAPEUTICS 499 (1978); William M. Wardell, *Introduction of New Therapeutic Drugs in the United States and Great Britain: An International Comparison*, 14 CLINICAL PHARMACOLOGY & THERAPEUTICS 773 (1973).

¹⁸ *FDA Approval of Drugs: Hearing Before the House Subcommittee on Oversight and Investigations, House Committee on Commerce*, 104th Cong. 1995 WL 331824 (F.D.C.H.) (May 25, 1995) (statement of Kenneth I. Kaitin, Ph. D., Associate Director, Tufts Center for the Study of Drug Development, Tufts University, Boston, Mass.).

tion—if not previously made public by the sponsor—was proprietary.¹⁹ It therefore should not, and under section 301(j) of the FDCA could not, be disclosed outside the Agency or relied on within the Agency to evaluate other (often competing) products.²⁰ This view embraced not only the technical information about how a product was designed and made—familiar trade secrets—but the reports of clinical studies that soon became the most expensive part of an NDA. And it extended across time to encompass the information about the progress of clinical studies that a drug sponsor is required under its IND to submit to FDA.²¹

FDA's position that the contents of NDAs (and antecedent INDs) are confidential has been criticized²² and occasionally challenged in court—but always, so far, without success.²³ Firms that are responsible for the development of new medicines rigorously defend the position, pointing out that the public release of the safety and effectiveness data in an NDA would allow competitors to free ride on their research and nullify their ability to recover the huge investments required to bring a new drug to market. Congress has accepted the FDA view in principle, and built a regime for approval of generic copies of innovative drugs around it.²⁴

FDA's long-standing, congressionally sanctioned policy of treating as confidential the reports of clinical studies of new drugs, and the existence of undisclosed applications that contain them, has special significance in the present context. New medical technologies, whose regulation may be at issue, sometimes attract attention for reasons that have little to do with their clinical safety or effectiveness. The debates over tissue transplants, gene therapy, and human cloning, to name just three examples, include questions about safety and medical utility, but they also embrace—indeed

¹⁹ See Merrill, *supra* note 10, at 1784.

²⁰ Hutt & Merrill Text, *supra* note 8, at 1301.

²¹ See 21 C.F.R. §§ 312.130, 601.51, 812.38 (2002).

²² Andrew Pollack, *Ex-Chief of ImClone Refuses to Testify To Congress About Testing of Drug*, N.Y. TIMES, June 14, 2002, at C1 (quoting Representative Billy Tauzin); Andrew Pollack, *House Panel to Investigate a Cancer Drug and its Maker*, N.Y. TIMES, January 19, 2002, at C1.

²³ *Anderson v. Dep't of Health and Human Servs.*, 907 F.2d 936 (10th Cir. 1990); *Webb v. Dep't. of Health and Human Serv.*, 696 F.2d 101 (D.C. Cir. 1982); *Pharm. Mfrs. Ass'n. v. Weinberger*, 401 F. Supp. 444 (D.D.C. 1975).

²⁴ Merrill, *supra* note 10, at 1792-1794; see generally *Drug Price Competition and Patent Term Restoration of 1984*, 35 U.S.C. § 156 (2000) ("Hatch-Waxman Act"); see also *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 861-62 (D.D.C. 1994) (opining that Congress intended Hatch-Waxman Amendments which govern FDA's approval of applications for generic versions of pioneer drugs to benefit pioneer drug manufacturers).

dramatize—questions of ethics, human autonomy, and societal values. Such issues are not the kind with which FDA routinely deals or in which it can claim real expertise, and their assessment, some argue, cannot be undertaken successfully if critical information about actual human experience cannot be widely shared.

Thus, questions about FDA's existing legal authority and institutional capacity to deal with new technologies inevitably implicate considerations of cost and access: Can innovation cope with the expense and time that seem inescapable parts of the traditional new drug approval process? Is a public dialogue about appropriateness and legitimacy possible when experimental data may not be disclosed?

II. FDA AND TISSUE TRANSPLANTS

Human tissue implants have been used in various kinds of surgery for more than two generations. A few early applications, e.g., corneal transplants, date from before World War II.²⁵ One product of the war itself was the Navy Tissue Bank, established in 1949,²⁶ which served as a repository for bone and skin from casualties of warfare, that were frozen and stored for use in treating survivors.²⁷ Until the early 1990's, however, FDA had essentially no role in regulating the recovery, processing, or clinical use of cadaver tissue. This was not because agency lawyers doubted FDA's legal authority to regulate tissues as either drugs, medical devices, or biologics. If FDA leaders had seized the authority agency lawyers advised was theirs, the medical use of tissue transplants might be much different. Many tissues would have been required to undergo some form of premarket review. The costs of securing approval would be substantial, and the time required would add years to the development. Communications between tissue banks and users—chiefly surgeons and the institutions where they work—would be subject to FDA's restrictions on labeling and promotion.

However, this picture does not resemble the world of tissue recovery, distribution and use that we observe today. And many,

²⁵ D.M. STRONG ET AL., *Impact of FDA Regulation on a Processor of Human Allograft Heart Valves*, 5 J. TRANSPLANT COORDINATION 9 (1995); Marc O. Williams, *The Regulation of Human Tissue in the United States: A Regulatory and Legislative Analysis*, 52 FOOD DRUG COSM. L.J. 409, 409-10 (1997).

²⁶ NATIONAL TISSUE BANK COUNCIL, POSITION PAPER CONCERNING THE REGULATION OF TISSUE AND TISSUE BANKS 6 (1991) [hereinafter NTBC POSITION PAPER].

²⁷ See *id.*

including some agency officials, undoubtedly believe that it is a good thing that FDA has not yet attempted to assert the full scope of its potential regulatory authority.

A. FDA Flirts with Regulating Tissue

The question whether FDA could regulate human tissue apparently first arose in 1973.²⁸ This was just a year after the old National Institutes of Health (NIH) Division of Biologics Standards became part of FDA under a new name, the Bureau for Biologics, and the FDA Commissioner acquired authority to administer relevant provisions of the Public Health Service Act.²⁹ This was an era when FDA rarely shrank from new challenges, and the response of the Chief Counsel to whom the question was first put, Peter Barton Hutt, was predictable: Human tissues *as well as* whole organs, could be considered "analogous" to materials such as blood, over which FDA had authority under section 351 of the Public Health Service Act.³⁰ Hutt went further:

In any event, whether human semen, human tissues and organs are or are not biological products, they clearly are drugs when used for therapeutic purposes or to affect any bodily function and accordingly are subject to the requirements of the FD&C Act. . . . The decision as to which Bureau within FDA handles these products is entirely an administrative matter that raises no legal issue.³¹

While there could hardly be a more emphatic endorsement of FDA's legal authority, Hutt does not appear to have addressed two other important questions: Was there a public health need for FDA to assert jurisdiction? This may not have been a question the Bureau thought it appropriate to ask to the Agency's lawyer, but the second question was surely within Hutt's competence: If tissue transplants were indeed drugs (and perhaps biologics too), could FDA fail to exercise regulatory jurisdiction? The Act's provisions governing premarket approval apply, by their terms, to any "new drug," defined as any drug that is not "generally recognized" by

²⁸ Stuart Nightingale, M.D., *Special Issue: The Regulation of Human Tissue and Organs*, 46 FOOD DRUG COSM. L.J. 4, 5 (1991).

²⁹ 42 U.S.C. 201-300 (2001).

³⁰ 42 U.S.C. § 262(i) (2002) ("In this section, the term 'biological product' means 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."); Nightingale, *supra* note 28, at 5.

³¹ *Id.*

qualified experts and safe and effective.³² Given its contemporary interpretation of that language, FDA could not plausibly have declared that tissues, however familiar, were generally recognized as safe and effective.

I have no evidence that Hutt's opinion was communicated outside the Agency or, indeed, widely distributed within it. Several years were to pass before FDA took any formal position regarding its authority to regulate tissue. This did not mean, though, that the subject was ignored. According to FDA's one-time Associate Commissioner for Health Affairs, Stuart Nightingale, representatives of the three bureaus (now "Centers") responsible for regulating medical products in 1976 "met to discuss possible regulation of tissue banks."³³ They apparently were not able to identify clear criteria that could justify and at the same time limit FDA's assertion of jurisdiction: "[N]o one system seemed applicable to all of the potential products that fall under the rubric of transplantable tissues. It was [therefore] decided that FDA jurisdiction over tissues would be asserted only in response to an immediate need."³⁴

Apparently FDA found no such "need" for over a decade.³⁵ Nightingale indicates, however, that the possibility of asserting jurisdiction was discussed earlier.

In 1979, two incidents occurred which led the agency to again review the possible need to regulate the banking of allogenic materials. In one incident, gonorrhea had been transmitted by contaminated fresh semen used in artificial insemination, and in the other incident a thirty-seven year old woman contracted rabies and died a month after she had received a corneal transplant.³⁶

Once again the question of legal authority was referred to FDA's Chief Counsel, then Richard Cooper, who declared that "any residual doubt about (FDA's) authority can be put aside," implying that whether and how to regulate were questions of science and pol-

³² 21 U.S.C. § 321(p)(1) (2001).

³³ Nightingale, *supra* note 28, at 5.

³⁴ *Id.*

³⁵ It was not until 1987 that the Agency first held that donated human tissue was subject to regulation - that year it advised distributors of *dura mater* that the material was considered to be a medical device which could only be distributed for investigational use. See, e.g., Nightingale, *supra* note 28, at 5-6; Jonathan Kahan, *FDA Regulation of Human Tissues Intended for Transplantation*, *Clinica Supp.* 1, 1 (1995) (describing history of *dura mater* regulation).

³⁶ Nightingale, *supra* note 28, at 5.

icy.³⁷ Once more, the decision was made not to assert jurisdiction. The reported incidence of disease transmission through transplantation was "extremely low."³⁸ Agency officials decided instead to support voluntary self-regulation by organizations that recovered and processed tissue, which had recently formed the American Association of Tissue Banks (AATB).³⁹ FDA officials reserved the possibility, if the need arose, of taking action on a case-by-case basis.⁴⁰ Significantly, foreshadowing steps the Agency was to take later, they believed "they could do so without first having to promulgate new regulations."⁴¹

In 1983 FDA for the first time addressed the question of its authority to regulate transplantable human tissue publicly.⁴² The specific question posed was whether the Agency had jurisdiction to regulate whole organs,⁴³ and it arose during hearings on what in 1984 became the National Organ Transplant Act, which established requirements for organ procurement organizations.⁴⁴ In a statement submitted to the House Subcommittee on Investigations and Oversight, FDA offered a cautious analysis of its possible sources of legal authority to regulate organ—and tissue—transplants.⁴⁵ FDA's statement was not read or referred to during the Agency's live testimony. Apparently it was solicited later by the committee. The statement explores each of three potential statutory sources of authority to regulate transplantable human material, but it displays none of the Agency's earlier confidence that its jurisdiction would be upheld. For example, in discussing the possibility that organs might fall within the FDCA's definition of "drug," FDA said:

A human organ . . . arguably could be regulated as a drug because it falls within the literal language of these provisions. . . . Such an interpretation, while arguably supportable, would extend the legal

³⁷ *Id.* (quoting Richard Cooper, General Counsel of FDA).

³⁸ *Id.*

³⁹ *Id.*

⁴⁰ Nightingale, *supra* note 28, at 5-6.

⁴¹ *Id.* at 6.

⁴² See generally *Statement by the Food and Drug Administration Concerning its Legal Authority to Regulate Human Organ Transplants and to Prohibit Their Sale: Hearing Before the Subcommittee on Investigations and Oversight, House Committee on Science and Technology, 98th Cong, 1st Sess. (1983)* [hereinafter 1983 FDA Statement to Congress].

⁴³ *Id.* (stating that "A human organ intended for use in transplantation arguably could be regulated as a drug because it falls within the literal language of these provisions.")

⁴⁴ Pub. L. No. 98-507, 98 Stat. 2339 (1984).

⁴⁵ The Agency's response drew no distinction between organs and other tissues.

definition well beyond the traditional medical concept of the term "drug." The unprecedented nature of this interpretation necessarily means that considerable uncertainty would be associated with a conclusion by FDA that the definition of the term "drug" includes human organ transplants.⁴⁶

The statement turned to the possibility that organs could be regulated as medical devices, acknowledging that "[a] human organ transplant could be regarded as within the literal language of the statute, for a transplanted organ is a type of 'implant.'"⁴⁷ But it went on to examine the sorts of implants that were discussed at the time the Medical Device Amendments were passed and concluded: "The legislative intent underlying the definition of 'device' is, therefore, probably limited to artificial implants," a conclusion for which the Agency found "further support . . . in the legislative history."⁴⁸

The statement's treatment of the possibility that organs might be considered "biological products" betrays similar caution. It begins with the PHSA's expansive listing of materials subject to regulation as biological products, examines the recent addition of human blood and blood components or derivatives, and concludes that the statute's vague catch-all, "analogous product," probably embraces only "analogous blood products" and not other human material procured for transplantation.⁴⁹ This is not language of an agency looking to take on new responsibility.

There undoubtedly were explanations for FDA's reticence. First, it should be emphasized that the hearings that elicited FDA's statement were focused on the procurement and allocation of whole organs.⁵⁰ Organ scarcity was, and remains, a paramount concern. A related concern was the potential for overreaching by organ procurement organizations.⁵¹ The risk of disease transmission, while recognized, was not viewed as serious.⁵² If FDA had no interest in becoming embroiled in regulating organ transplants, expressing doubt about its legal authority was surely prudent.

⁴⁶ 1983 FDA Statement to Congress, *supra* note 42.

⁴⁷ At that time, the Act defined device as "an instrument, apparatus, implement, machine, contrivance, *implant*, in vitro reagent, or other similar or related article. . . ." Medical Device Amendments of 1976, § 3, 90 Stat. 539 (1976) (current version at 21 U.S.C. § 321(h) (2001)) (emphasis added).

⁴⁸ 1983 FDA Statement to Congress, *supra* note 42.

⁴⁹ *Id.*, citing 42 U.S.C. § 262(i) (2001).

⁵⁰ 1983 FDA Statement to Congress, *supra* note 42.

⁵¹ See Nightingale, *supra* note 28, at 6.

⁵² See *id.* at 5.

Accordingly, one should not infer from FDA's 1983 statement that officials had come to believe that the Agency lacked authority to regulate human tissue transplants. What they really believed is probably not important. What is important is that the statement suggested that FDA would not soon attempt to extend its authority to regulate materials recovered from cadaver donors for transplantation. Yet, within the decade, FDA had asserted jurisdiction over a number of tissues used in surgery.⁵³

What caused FDA to venture into this arena? The primary explanation was the discovery that tissues could transmit infectious disease from the donor to transplant recipients.

Issues such as whether or not allogeneic tissue was processed, or to what degree it was processed, or to what extent it was commercialized, became less and less important a reason to regulate as the threat of communicable disease loomed larger. . . . Much of what was being learned about the potential infectivity of blood and plasma was applicable to other bodily fluids, as well as to organs and tissues. . . . [O]ther factors caused FDA to reevaluate its policy toward transplantation. One incident involved the apparent transmission of Creutzfeldt-Jakob disease by an allograft of dura mater. . . . FDA became increasingly concerned about the safety of donor semen and breast milk. . . . During the 1980s it became clear that FDA needed to respond to threats to the public health posed by tissues such as corneal lenticules, dura mater, and human heart valves that were being used in ways closely related to products that have traditionally been regarded as and regulated as biologics or medical devices. For the most part this meant undertaking active measures to prevent transmission of communicable diseases in areas where tissue was being transplanted and body fluids . . . were being used.⁵⁴

By 1990 FDA had asserted regulatory jurisdiction over dura mater and corneal lenticules.⁵⁵ It had signaled processors of human heart valves that it was likely to regulate their products as Class III medical devices, for which premarket approval would be required.⁵⁶ FDA was clearly becoming concerned about the growing uses of allogeneic tissue. According to Nightingale, Agency officials were in communication with providers of tissue and their organizational

⁵³ For examples of FDA's case-by-case approach to regulation of tissue transplants, see Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products, 63 Fed. Reg. 26,744 (May 14, 1998); see also, e.g. Cardiovascular Devices; Effective Date of Requirement for Premarketing Approval; Replacement Heart Valve, 52 Fed. Reg. 18,162 (May 13, 1987).

⁵⁴ Nightingale, *supra* note 28, at 6-8.

⁵⁵ See Kahan, *supra* note 35, at 1.

⁵⁶ *Dura Mater Reprocessors about to be Regulated as Device Manufacturers*, M-D-D-I REP., July 16, 1990, at 7, 8.

representatives, expressing concern about the risk of disease transmission generally and about AIDS particularly.⁵⁷ The main thrust of these communications, however, was hortatory. FDA was generally prepared to rely on self-policing, augmented by official recommendations from the Centers for Disease Control (CDC) about improved methods for disease testing and tightened criteria for donor eligibility.⁵⁸

B. FDA's Reluctance to Assert Jurisdiction

FDA never seized upon the advice of two Chief Counsels, who advised that the Agency *could* regulate tissues as it regulated other medical products. It seems unlikely that FDA officials questioned this advice. FDA's 1983 statement to Congress acknowledged that organs could conceivably be regulated as drugs, as medical devices, or as biological products.⁵⁹ Congress may *not* have had human tissues in mind when it enacted the relevant definitions, but general statutory provisions are frequently extended to technologies that had not been developed when the laws were enacted.⁶⁰ FDA itself had been successful in gaining judicial approval for expansive interpretations of its chartering legislation.⁶¹

Although human tissues could be considered "drugs" under FDCA, the Act's definition of "device" probably better captures the way in which most tissues are used in surgery. The FDCA defines "device" as "an instrument, apparatus, implement, machine, contrivance, *implant*, in vitro reagent, or other similar or related article . . . which is . . . intended for use in the . . . cure, mitigation, treatment, or prevention of disease" or which is "intended to affect the structure of any function of the body," and "which does not achieve any of its principal intended purposes through chemical action within or

⁵⁷ Nightingale, *supra* note 28, at 7-8.

⁵⁸ *Id.* (discussing a joint report issued by the FDA and CDC which "recommended that unless the semen is from a donor who is in a mutually monogamous marriage/relationship with the recipient, it should be frozen and used only if tests of the donor's semen at the time of the donation and again six months later are negative for HIV antibodies.").

⁵⁹ 1983 FDA Statement to Congress, *supra* note 42.

⁶⁰ For example, FDA has asserted regulatory authority over cloning, gene therapy, and umbilical cord blood, and the FTC now regulates advertising on the internet using statutory language developed with radio, television, and traditional print sources in mind. *See, e.g.*, Lawrence M. Hertz, *Advertising Regulation on the Internet*, 19 *COMPUTER AND INTERNET LAWYER*, June 2002, at 18-19.

⁶¹ *See, e.g.*, *United States v. An Article of Drug . . . Bacto-Unidisk . . .*, 89 S. Ct. 1410, 1415 (1969).

on the body."⁶² This language could embrace most current medical uses of human tissue.

FDA's counsel were therefore on sound ground when they advised that the Agency could successfully assert jurisdiction over tissues if it saw a need to do so. Nightingale records that during the 1980s some officials were of the view that the Agency was obliged to regulate tissue.⁶³ They may have recognized that tissue transplants were being used for purposes identical to those for which man-made—and comprehensively regulated—products were being used. Heart valve allografts were an example. Artificial replacement heart valves had been in use prior to 1976. Indeed, they were mentioned in the legislative history of the 1976 Medical Device Amendments as an example of a technology that should be more effectively regulated.⁶⁴ Porcine heart valves were also being transplanted into humans, and they, too, were generally acknowledged to fall within FDA's jurisdiction.⁶⁵ To leave replacement valves recovered from human donors unregulated could have seemed anomalous.

Others recognized, however, that regulating by analogy would have far-reaching implications. The statutory definition of "device" is very broad.⁶⁶ It would not be easy to confine regulation to tissue implants that resembled artificial products designed for similar use. Even with such a limitation, FDA would suddenly be responsible for a large number of tissues with a wide variety of surgical applications, few of which the Agency's staff understood well. Most tissues are ordered by surgeons and implanted in patients under their immediate supervision. Furthermore, many forms of tissue now offered by tissue banks were devised by, or prepared according to instructions from, implanting surgeons.⁶⁷ It would have been difficult for FDA to regulate the activities of tissue banks without encroaching on the judgments and activities of surgeons themselves.

⁶² 21 U.S.C. § 321(h) (2001) (emphasis added).

⁶³ Nightingale, *supra* note 28, at 8.

⁶⁴ S. REP. NO. 94-33, at 5 (1976), *reprinted in* 1976 U.S.C.C.A.N. 1070, 1074.

⁶⁵ *See* Cardiovascular Devices; Effective Date of Requirement for Premarket Approval; Replacement Heart Valve Allograft, 56 Fed. Reg. 29,177-78 (June 26, 1991) [hereinafter Heart Valve Allograft Rule].

⁶⁶ 21 U.S.C. § 321(h) (2002).

⁶⁷ Ronald C. Elkins, *Special Issue: The Regulation of Human Tissue and Organs*, 46 *FOOD DRUG COSM. L.J.* 35, 35 (1991); Comments from American Association of Tissue Banks to Dockets Management Branch of Food and Drug Administration 1 (March 14, 1994) [hereinafter AATB Comments].

Furthermore, the requirements FDA would be obliged to impose if tissues were drugs or medical devices did not seem well-matched for the operations of tissue recovery and processing or well-suited to address the concerns that might justify regulation in the first place. If human tissues were "drugs," virtually every one would be a "new drug" for which FDA approval was required. Few tissue banks had the resources to fund the sort of clinical studies that FDA would require.⁶⁸ Moreover, a declaration that tissues – or some tissues – are "new drugs" would seem to require that the Agency take steps to prevent their continued distribution until approval could be sought and granted.⁶⁹

Classifying tissues as "devices," would also present problems for FDA. Not all medical devices require premarket approval by FDA; only those classified in Class III, and then only after the Agency calls for applications.⁷⁰ The device law would thus appear to afford a "window" during which suppliers could conduct the studies needed to gain Agency approval. But this avenue was available only for devices that were in commercial distribution prior to 1976 or were "substantially equivalent" to a device then in distribution.⁷¹ For any tissue first provided to surgeons after 1976, it would have been difficult for FDA to fashion even a temporary exemption from the Act's premarket approval requirement.

This is not to say that FDA officials were unconcerned about the risks posed by unregulated tissue transplants during the 1980s. Three developments would eventually lead the Agency to take a more forceful role. Without question the most important of these was the mounting public and professional concern about AIDS. FDA officials confronted the grim reports of a growing epidemic primarily in two contexts. First, the Agency's costly requirements for approval of new drugs came under sharp attack from AIDS patients and caregivers.⁷² The other arena in which AIDS posed a spe-

⁶⁸ Williams, *supra* note 25, at 416.

⁶⁹ See, e.g., *Regulation of Medical Devices (Intrauterine Contraceptive Devices): Hearings Before the Intergovernmental Relations Subcommittee of the House Committee on Government Operations*, 93d Cong., 1st Sess. (1973), reprinted in Hutt & Merrill Text, *supra* note 8, at 734 ("[W]ithout new legislation . . . we would have been in a very difficult position to try to catch up with history in regulating 'IUDS.'").

⁷⁰ Hutt & Merrill Text, *supra* note 8, at 751 (2d ed. 1991).

⁷¹ 21 U.S.C. § 360e(b)(1) (2001).

⁷² Hutt & Merrill Text, *supra* note 8, at 552. The story of the Agency's response, intended to speed approval of promising therapies and allow broader access to those in clinical trials, has been recounted elsewhere. See, e.g., AIDS, Experimental Drug Approval, and the FDA

cial challenge was the country's system for collecting, processing, and distributing whole blood and blood products, for which FDA had assumed regulatory responsibility in 1972.⁷³ By the middle of the 1980's, at least,⁷⁴ it had become clear that the HIV virus could be transmitted by transfused blood and some processed blood products. FDA, together with the Centers for Disease Control, took a series of measures to reduce this risk.⁷⁵ The government's efforts to protect the blood supply focused on two strategies that were soon to become centrally relevant in discussions of whether and how human tissues should be regulated.

One involved measures to screen out potential blood donors whose physical condition or personal habits suggested that they might be infected by, or were at high risk for, HIV.⁷⁶ The second strategy was to discover, perfect, and direct the adoption of methods for testing donated blood and processed blood products for the presence of the virus.⁷⁷ Once it became clear that HIV could be transmitted through transplanted human tissue, the same strategies had obvious relevance for those engaged in distributing tissue—and for the Agency with potential authority to regulate them.⁷⁸ Concern about disease transmission thus became the primary justification for FDA's creation of a system for tissue regulation in December 1993.

C. FDA Ventures into the Tissue Arena

Even before 1993, however, FDA had selectively asserted its authority to regulate tissue-based products. For example, in 1989 FDA announced that corneal lenticules were to be regulated as Class III medical devices for which Premarket Approval Applications (PMAs) would be required.⁷⁹ The lenticules were the product of a new process in which cadaver corneas were freeze-dried,

New Drug Screening Process, 2 NYU J. LEGIS. & PUB. POL'Y 295 (1999-2000); see also Mary M. Dunbar, *Shaking Up the Status Quo: How AIDS Activists Have Challenged Drug Development and Approval Procedures*, 46 FOOD DRUG COSM. L.J. 673 (1990-1991). See also *How the AIDS Crisis Made Drug Regulators Speed Up*, N.Y. TIMES, Sept. 24, 1989, at E5.

⁷³ 21 C.F.R. § 606 (2002).

⁷⁴ INSTITUTE OF MEDICINE, HIV AND THE BLOOD SUPPLY: AN ANALYSIS OF CRISIS DECISIONMAKING 20, Lauren Leveton et al., eds. (1995) [hereinafter IOM Report].

⁷⁵ *Id.*

⁷⁶ *Id.* at 73.

⁷⁷ *Id.* at 77-78.

⁷⁸ Human Tissue Intended for Transplantation, 58 Fed. Reg. 65,514 (Dec. 14, 1993).

⁷⁹ Memorandum from Gregory J. Glover 2 (Nov. 7, 1989) (on file with Houston Journal of Health Law & Policy) [hereinafter Glover Memorandum].

ground, and stored.⁸⁰ The resulting products closely resembled contact lenses, which FDA had long regulated.⁸¹

Grafts of dura mater, the tough lining covering the brain and spinal cord,⁸² have been used, albeit sparingly, by neurosurgeons for many years. In the mid-1980s, a patient who had received a dura mater graft was diagnosed with Creutzfeldt-Jakob disease, later traced to the graft donor. FDA promptly declared that "dura mater of human origin is subject to regulation as a device."⁸³ The Agency advised the few distributors of dura mater that they would need to comply with the FDCA provisions applicable to devices, including registration, product listing, and compliance with good manufacturing practices (GMP) regulations.⁸⁴ Further, the Agency held, each distributor was obliged to submit a premarket notification that would demonstrate it had been distributing the tissue prior to the enactment date of the 1976 Medical Device Amendments.⁸⁵ It is unclear how many tissue banks responded to FDA's demands. What is clear is that no bank challenged either FDA's determination that dura mater was a medical device or the abrupt manner in which the Agency announced its decision.

Thus, by mid-1991, FDA had asserted jurisdiction over four different types of human tissue, in each instance relying on the FDCA requirements for medical devices. No tissue bank disputed the Agency's jurisdiction or challenged its declaration that the device law was the appropriate mechanism. In no case does it appear that FDA's intervention caused any bank to cease operations or interrupt distribution of the tissue that the Agency sought to regulate.

A common feature of these actions was their low visibility. FDA avoided publication in the *Federal Register*, and thus never offered a formal analysis of its legal authority or the need for regulation. This left tissue banks largely in the dark (if on edge) about the Agency's regulatory plans. Occasionally, an FDA official provided

⁸⁰ *Id.*

⁸¹ See Hutt & Merrill Text, *supra* note 8, at 770.

⁸² Robert E. Hair & David Polin, *Spinal Cord Injuries*, 37 AM. JUR. Proof of Facts 2d §291 (2001).

⁸³ Kahan, *supra* note 35, at 1 (1995); *Dura Mater Reprocessors about to be Regulated as Device Manufacturers*, *supra* note 56, at 7; "Dear Sir/Madam" Letter from Leighton W. Hansel, Division of Produce Surveillance, Center for Devices and Radiological Health, Food and Drug Administration, (Nov. 14, 1990).

⁸⁴ *Id.*

⁸⁵ *Id.* Like FDA's decision regarding corneal lenticules, this ruling was never published in the *Federal Register*.

a clue as to its reasoning. For example, according to Dr. David L. West, Deputy Director of the Office of Device Evaluation, the "current thinking" of agency staff was that FDA should—and perhaps under the law must—regulate processed human tissues "that closely resemble a device."⁸⁶

D. FDA's Effort to Regulate Human Heart Valves

In June 1991 FDA announced—this time in the *Federal Register*⁸⁷—that it was asserting jurisdiction over heart valve allografts.⁸⁸ Surgery to replace defective heart valves had become a common procedure in many countries, including the United States by the 1970s.⁸⁹ A variety of replacement valves combining various materials had been developed and come into use. Porcine heart valves had also gained popularity for certain procedures.⁹⁰ From the enactment of the 1976 Medical Device Amendments, officials in FDA's Bureau of Medical Devices (now the Center for Devices and Radiological Health) made clear that they believed that the risks associated with, and the uncertainty about the utility of, these implants warranted rigorous regulation. Under the statute this meant that they would fall in Class III, which in turn meant that each type would require premarket approval.⁹¹

In the particular context, of course, "premarket approval" was an oxymoron because the replacement heart valves that FDA undertook to regulate after 1976 were already lawfully marketed, albeit without agency approval. What the Amendments did for pre-enactment Class III devices was empower FDA to require the submission of clinical data, confirming their safety and effectiveness. In 1979 FDA commenced the statutory procedures to trigger this obligation for what it termed "replacement heart valves."⁹² Another decade

⁸⁶ Glover Memorandum, *supra* note 79, at 1-2.

⁸⁷ Heart Valve Allograft Rule, *supra* note 65.

⁸⁸ See *id.*

⁸⁹ NTBC POSITION PAPER, *supra* note 26, at 38.

⁹⁰ Cardiovascular Devices: Classification of Replacement Heart Valves, 45 Fed. Reg. 7,948 (Feb. 5, 1980); Medical Devices; Classification of Replacement Heart Valves, 44 Fed. Reg. 13,387, 13,388 (Mar. 9, 1979).

⁹¹ 21 U.S.C. § 360c(a)(1)(C) (2001).

⁹² Medical Devices; Classification of Replacement Heart Valves, 44 Fed. Reg. 13,387 (Mar. 9, 1979).

passed, however, before the Agency showed concern about a third type of heart valve, those derived from cadavers.⁹³

1. Requiring Premarket Approval

The 1976 Amendments required FDA, before it undertook regulation of individual products, to classify all the devices then on the market, assigning each type to one of three tiers of regulatory control.⁹⁴ Premarket approval was contemplated for only a small minority of devices, but "implants" were prime candidates for this status, known as Class III.⁹⁵ Under the FDCA, classification was a three-stage process, commencing with a recommendation by an expert advisory committee, followed by *Federal Register* publication of FDA's proposed classification with an opportunity for comment, and concluding with publication of a final classification rule.⁹⁶ For a device placed in Class III, FDA then had to complete two additional steps before it could demand submission of (formal) marketing applications: it had first to publish a proposed "call" for PMAs, affording an opportunity for requests that the device be reclassified, and then, later, to promulgate a final regulation setting a deadline for submission of PMAs.⁹⁷

The law prescribes a schedule for this to occur.⁹⁸ FDA may not demand the submission of PMAs for any Class III device earlier than 30 months after classification or less than 90 days following promulgation of a regulation mandating submission of PMAs.⁹⁹ In other words, manufacturers of Class III devices were to have *at least* 30 months after classification in which to assemble data demonstrating their safety and effectiveness.¹⁰⁰ In the meantime, the devices could remain in commercial distribution and in clinical use.¹⁰¹

FDA followed a more relaxed timetable with "replacement heart valves." In 1979, the Agency published proposals to classify a

⁹³ See Heart Valve Allograft Rule, *supra* note 65.

⁹⁴ 21 U.S.C. § 360c(b)(1) (2001).

⁹⁵ See H.R. Rep. No. 94-1090, at 1104-1105, 1107 (1976).

⁹⁶ See 21 U.S.C. §§ 360c(c)-(d), (f) (2001).

⁹⁷ 21 U.S.C. § 360c(e) (2001).

⁹⁸ Medical Device Amendments of 1976, Pub. L. No. 94-295, 1976 U.S.C.A.N. 1070, 1093-98.

⁹⁹ 21 U.S.C. § 351(f)(2)(B) (2001); 21 U.S.C. § 360e(b)(1) (2001).

¹⁰⁰ 21 U.S.C. § 351(f)(2)(B) (2001); 21 U.S.C. § 360(e)(1) (2001).

¹⁰¹ 21 U.S.C. § 360j(l)(3)(A) (2001).

large number of devices—including "replacement heart valves."¹⁰² The Agency described "replacement heart valves" as "a device intended to perform the function of any of the heart's natural valves. . . [including] valves constructed of prosthetic materials, biologic valves (e.g. porcine valves), or valves constructed of a combination of prosthetic and biologic materials."¹⁰³ The *Federal Register* notice did not mention human heart valves, and the Agency never suggested that the advisory panel on whose advice it relied had considered them. This proposal did not prompt a single comment, and a year later the Agency published a final rule confirming its classification.¹⁰⁴ The preamble to this rule did not mention human heart valves.¹⁰⁵

Why are the details of FDA's documents important? Eleven years later the Agency would take the position that its initial steps toward requiring PMAs for "replacement heart valves" applied to human heart valves as well as to mechanical and porcine valves.¹⁰⁶ To be fair, FDA never said that its 1979 and 1980 documents applied to human heart valves; the document whose application the Agency later defended was not published until 1987. This document was a final rule requiring the makers of "replacement heart valves" to submit PMAs within 90 days.¹⁰⁷ But there is no evidence that the term "replacement heart valves" had a different meaning in 1979. Moreover, the Agency could not concede that the 1979 and 1980 documents might not have covered human valves. If they did not, human valves had not yet been classified and could not be regulated as Class III devices, unless they were first introduced after 1976, which FDA never claimed.

Although publication of the 1980 final classification rule put makers of "replacement heart valves" on notice that some day FDA would call on them to submit PMAs, the rule did not immediately

¹⁰² Classification of Cardiovascular Devices, 44 Fed. Reg. 13,284 (Mar. 9, 1979) (codified at 21 C.F.R. pt. 870.1); Medical Devices: Classification of Replacement Heart Valves, 44 Fed. Reg. 13,387 (Mar. 9, 1979) (codified at 21 C.F.R. pt. 870.3925).

¹⁰³ Medical Devices; Classification of Replacement Heart Valves, 44 Fed. Reg. 13,387, 13,388 (Mar. 9, 1979) (codified at 21 C.F.R. pt. 870.3925).

¹⁰⁴ Medical Devices; Classification of Replacement Heart Valves, 45 Fed. Reg. 7,948 (Feb. 5, 1980) (codified at 21 C.F.R. pt. 870.3925).

¹⁰⁵ *Id.*

¹⁰⁶ See Heart Valve Allograft Rule, *supra* note 65.

¹⁰⁷ Cardiovascular Devices; Effective Date of Requirement for Premarketing Approval; Replacement Heart Valve, 52 Fed. Reg. 18,163 (May 13, 1987) (codified at 21 C.F.R. pt. 870.3925(c)).

alter their marketing status. FDA did not publish its proposal to call for PMAs until February 12, 1986, in a document addressed to manufacturers of "replacement heart valve[s]," whose function and characteristics it went on to describe:

The replacement heart valve is a device intended to perform the function of any of the heart's natural valves, and is used when one (or more) of the natural heart valves is diseased, damaged, or malfunctioning. . . . The replacement heart valve includes valves constructed of prosthetic materials, biologic materials (e.g., porcine valves), or valves constructed of a combination of prosthetic and biologic materials. The configuration of replacement heart products varies a great deal, and the design of a particular valve product is of importance in its effectiveness, as well as the complication rate observed.

In general, the replacement heart valve consists of a housing that is surgically affixed in the heart and a movable portion that performs the valve function, permitting unidirectional blood flow only. Materials used in the device should meet a generally accepted satisfactory level of tissue and blood compatibility, including requirements for adequate surface finish and cleanliness, which may affect the degree of compatibility. Performance characteristics, including blood flow properties and mechanical strength, should be maintained at a generally accepted satisfactory level and should be made known to the user [i.e., the transplant surgeon] through special labeling.¹⁰⁸

FDA's preamble then proceeded to analyze the risks and uncertainties associated with replacement heart valves.¹⁰⁹

The critical question, eventually, was whether this document applied to heart valves from human donors. The document itself did not mention human heart valves. The word "allograft" did not appear. Nor did the word "tissue." The scientific references that FDA cited in support of its proposal dealt with the use of mechanical or porcine valves.¹¹⁰ Notably, FDA's discussion of the risks associated with valve replacement did not mention the possibility of transmission of infectious disease.¹¹¹

FDA's proposal to require PMAs generated no more controversy than its earlier decision to classify replacement valves in Class III. The Agency received just one comment, which did not address

¹⁰⁸ Cardiovascular Devices; Premarket Approval of the Replacement Heart Valve, 51 Fed. Reg. 5,296, 5,297 (Feb. 12, 1986) (codified at 21 C.F.R. pt. 870.3925(c)).

¹⁰⁹ 51 Fed. Reg. at 5,297-99.

¹¹⁰ 51 Fed. Reg. at 5,299-300.

¹¹¹ 51 Fed. Reg. at 5,297 (A close reading of FDA's description of replacement heart valves, quoted above, suggests that it was primarily concerned with valves constructed or fashioned by human ingenuity. It employs words like "constructed," "design," "product," "housing," "materials," and "maintenance of blood flow characteristics.").

the scope of the proposal.¹¹² No one inquired whether, or expressed concern that, it might apply to human heart valves, and not surprisingly FDA's final rule did not mention that possibility. Distributors of "replacement" valves were required to submit PMAs by December 9, 1987, and to have received approval no later than June 6, 1988.¹¹³

The half dozen tissue banks that processed human heart valves made no effort to comply with FDA's requirements. It is unclear whether they were even aware of FDA's announcement. None had previously registered with FDA as a manufacturer or distributor of devices.

2. FDA's Concern for Human Heart Valves

In June 1991, FDA published in the *Federal Register* an announcement¹¹⁴ that PMA's were required for the continued distribution of *human* heart valves. The Agency asserted that human valves were covered by its 1987 rule requiring PMAs for "replacement heart valves," and set forth an accelerated schedule for compliance.¹¹⁵ This action led, ultimately, to a pair of lawsuits challenging the Agency's action and the procedure it had followed.¹¹⁶

It is not easy to reconstruct the events leading to FDA's announcement in June 1991. Certain statements can be ventured with a high degree of confidence, but others are speculation. It is arguable that FDA did not have a position on whether PMAs were required for human heart valves until its announcement to that effect in June 1991. In that document, however, the Agency claimed that its 1987 call for PMAs had always applied to human heart valves.¹¹⁷ For legal purposes it was not imposing a new requirement but merely explaining a requirement already in effect.

This rationalization is difficult to reconcile with previous statements made, or not made, by FDA officials. Those statements and

¹¹² This lone comment is described in the May 1987 *Federal Register*. Cardiovascular Devices; Effective Date of Requirement for Premarket Approval; Replacement Heart Valve, 52 Fed. Reg. 18,162, 18,162 (May 13, 1987).

¹¹³ 52 Fed. Reg. at 18,163.

¹¹⁴ Not a "rule," but not published in the "Notices" segment of the *Federal Register* either. Heart Valve Allograft Rule, *supra* note 65.

¹¹⁵ *Id.* at 29,178-79.

¹¹⁶ See *infra*, Part II-D-5.

¹¹⁷ Heart Valve Allograft Rule, *supra* note 65, at 29,178. "It has been clear for some time that FDA intended to regulate human heart valves as replacement heart valves, subject to the Agency's 1987 PMA requirement." *Id.*

silences suggest a less tidy deliberative process. First, as to the silences, there is no evidence that any responsible FDA official at the time thought, much less said, that the 1987 call for PMAs for "replacement heart valves" applied to human heart valves. This is not to say that agency officials believed that the 1987 rule *could not* apply to human valves. Their silence is consistent with not having considered the possibility. This oversight alone might not defeat the Agency's later claim that the terms of the rule were broad enough to embrace human heart valves.¹¹⁸

The more interesting question is what caused FDA officials to become so concerned about human heart valves that they decided, four years later, that the 1987 rule should be interpreted as covering them. It is clear that some time between 1987 and late 1990 FDA officials became convinced that the Agency would have to regulate human heart valves—along with other replacement valves. The question is why. According to Dr. David West, quoted above, some agency officials were uncomfortable with its failure to regulate processed tissues that performed the same function as man-made devices.¹¹⁹ But this view surely is not the complete, and perhaps not even the primary, explanation. It appears that FDA officials concluded that allograft valves should be regulated *in some fashion* before they had decided that PMAs should be required, and thus before agency lawyers devised the theory that human heart valves already were covered by the 1987 rule. In early 1991 a story broke suggesting that tissue transplants could pose serious risks for transplant recipients.

3. Human Tissues and HIV

In 1985 the family of a 22-year old Virginia man, who had died from gunshot wounds, agreed to donate his organs and tissues for transplantation.¹²⁰ Tests of the donor for HIV were negative. His

¹¹⁸ Richard J. Pierce, *ADMINISTRATIVE LAW TREATISE* VOL. I 425-426, 496 (4th Ed. 2002). "The vast bulk of challenges to the adequacy of agency notices of proposed rulemaking fall into one of two categories: (1) the divergence between the proposed action and the final action was so great that parties affected by the final action had no way of knowing that the Agency was considering one or more critical elements of the final action; or (2) the Agency relied on data to support its final action that was not known to affected parties until the Agency announced its final action. Both arguments are premised on the same reasoning: Parties cannot submit meaningful comments unless they know the issues under consideration by the Agency." *Id.*

¹¹⁹ See Glover Memorandum, *supra* note 79.

¹²⁰ RJ SIMONDS ET AL., *Transmissions of Human Immunodeficiency Virus Type 1 from a Seronegative Organ and Tissue Donor*, 326 *NEW ENG. J. MED.* 726, 726-32 (March 12, 1992).

tissues were processed and distributed by LifeNet Transplant Services of Virginia Beach.¹²¹ Over the next few years several dozen individuals received grafts from the Virginia donor.¹²² Some time thereafter seven of them tested positive for the HIV antibody.¹²³ Their infections were attributed to the common donor, who at the time he died had been infected but apparently fell within the "window" between exposure to the AIDS virus and the development of detectable antibodies.¹²⁴

The message for FDA was clear. The AIDS virus could be transmitted through non-vascularized human tissue, just as it could be communicated through transfusion of whole blood or the administration of processed blood products. It was probably this discovery that spurred FDA to declare that allograft heart valves were Class III "replacement heart valves" that, under its 1987 rule, required PMAs.¹²⁵ The Agency could not, however, emphasize the risk of communicable disease in explaining this decision because its legal theory was that the decision had been reached in 1987.

I cannot be positive that the LifeNet episode was the prime motivator for FDA, but one element of the Agency's decision suggests that it was. The legal consequence of FDA's June 1991 announcement should have been that distributors of allograft heart valves were subject to the same schedule for submitting PMAs as the makers of artificial valves. However, this would have meant that the deadline for compliance had long since passed, since FDA's original rule allowed only 90 days for the valve makers to submit PMAs.¹²⁶ FDA devised an escape from the draconian consequences of its own legal theory; it ultimately accorded the allograft valve processors nearly a year in which to either secure approval of PMAs or limit their distribution of allograft valves to approved investigational trials.¹²⁷ But the Agency was not willing to allow the allograft processors as much time as their competitors to collect data and

¹²¹ NTBC *Position Paper*, *supra* note 26, at 18.

¹²² *Id.*

¹²³ John Henkel, *Safeguarding Human Tissue Transplants*, *FDA CONSUMER*, Sept. 1, 1994.

¹²⁴ NTBC *Position Paper*, *supra* note 26, at 18.

¹²⁵ This declaration was made formally in the June 1991 *Federal Register*. Heart Valve Allograft Rule, *supra* note 65.

¹²⁶ Cardiovascular Devices; Premarket Approval of the Replacement Heart Valve, 51 *Fed. Reg.* 5,296-97 (Feb. 12, 1986).

¹²⁷ Cardiovascular Devices; Extension of Effective Date of Requirement for Premarket Approval; Replacement Heart Valve Allograft, 56 *Fed. Reg.* 35,815 (July 29, 1991).

submit applications. This was a major source of frustration for the processors and appears to have come as a surprise as well.

FDA's June 1991 announcement was not the first time the processors learned of FDA's concerns. Agency representatives had informally hinted that they would ultimately expect PMAs for allograft valves, but not until December 1990 were there indications that the Agency might hold that the clock had started back in 1987.¹²⁸ By then, however, it appears that FDA officials, led by a new Commissioner, Dr. David Kessler, had reached two decisions. First, the decision to demand PMAs for allograft heart valves was firm.¹²⁹ Second, as Agency spokesmen acknowledged in congressional testimony, FDA lawyers had concluded that the Agency could interpret the 1987 rule calling for PMAs for "replacement heart valves" as imposing this requirement on processors of allografts.¹³⁰

4. FDA's Decision

FDA's June 16, 1991 announcement was titled a "Notice of applicability of a final rule."¹³¹ The document asserted that allograft valves were "replacement heart valves" subject to the Agency's 1987 rule, which required that after June 1988 all replacement heart valves have PMAs or be distributed only under approved IDEs.¹³²

FDA officials must have recognized that they were taking some legal risk in declaring that allograft heart valves were subject to a rule that no one, at the time it was promulgated, knew applied to them. The Agency's preamble justified this "expedited" procedure in two ways. First, it sought to draw the sting from an anticipated lack-of-notice objection by recounting several exchanges between Agency representatives and the valve processors, even though, by FDA's own account, these discussions did not commence until 1989, two years after its rule was published.¹³³

Second, FDA's discussion was chiefly devoted to supporting its assertion that the 1987 rule, on its face, applied to human, as well as to mechanical and porcine, heart valves.

¹²⁸ Johnson, *infra* note 149, at 31.

¹²⁹ D.M. STRONG ET AL., *supra* note 25, at 10.

¹³⁰ See generally, *id.*

¹³¹ Heart Valve Allograft Rule, *supra* note 65.

¹³² Cardiovascular Devices; Effective Date of Requirement for Pre-market Approval; Replacement Heart Valve, 52 Fed. Reg. 18,162, 18,163 (May 13, 1987).

¹³³ Heart Valve Allograft Rule, *supra* note 65, at 29,178.

... [A] replacement heart valve allograft is intended to perform the function of any of the recipient's natural heart valves. Replacement heart valve allografts, by definition, are constructed of biologic materials in that they are human heart valves which are processed to assure shelf life and suitability for transplantation in a recipient. There can be little question that the classification regulation for replacement heart valves, when construed to achieve the act's purpose of protecting the public health, must include replacement heart valve allografts.

Both the classification regulation and the regulation requiring premarket approval applications clearly demonstrate FDA's intent to subject all replacement heart valves to the agency's premarket approval process. . . .

If . . . the valves were considered apart from the existing classification regulation, and shown to be a preamendment device, then they would not be subject to FDA's assessment of safety and effectiveness for years. This view could only be based on a stilted, unrealistic reading of the classification regulation, and would be inconsistent with FDA's public health purpose.

... [I]f the valves were viewed as a unique preamendment device, replacement heart allografts legally would not in the interim be subject to any greater regulatory oversight than devices with little or no risk. This result is clearly inadequate to regulate a device that can raise significant safety concerns, including causing the transmission of the acquired immunodeficiency syndrome virus. . . .¹³⁴

The last clause is the only reference to the risk that animated FDA's decision to require PMAs for human heart valves. Other questions went unaddressed. Why, if heart valves were medical devices, were not all transplantable human tissues? If processors were distributing a medical device, why had they never been required to register with FDA, as the FDCA requires of all device distributors?¹³⁵

From FDA's perspective, if the 1987 rule did cover allograft valves, the Agency rebutted any claim that it had not followed proper procedures. For it had undeniably followed the statutorily prescribed procedures in issuing the rule. FDA's legal theory had another consequence, of which its lawyers must surely have been aware. If the 1987 rule obligated the heart valve processors to submit PMAs, their opportunity to challenge this directive in court had long since passed. The FDCA only permits preenforcement judicial review of section 515(b) rules within 60 days of promulgation.¹³⁶

¹³⁴ *Id.*

¹³⁵ 21 U.S.C. § 360 (2001).

¹³⁶ 21 U.S.C. § 335b(c) (2001). Furthermore, as counsel would later argue, FDA's rule could not be challenged in any other proceeding because the Act's provision for judicial review was exclusive. See Medical Device Amendments of 1976, Pub. L. No. 94-295, 1976 U.S.C.A.N. 1070, at 1081, 1085, 1091.

The immediate reaction of the tissue banks that distributed heart valves was to seek an extension of FDA's deadline.¹³⁷ The Agency granted a delay until November 25, 1991.¹³⁸ However, it never agreed to allow the full 30 months that the Act guaranteed and that the makers of artificial valves had enjoyed. This was the principal injury the banks suffered as a result of FDA's peremptory action, but it was not the only problem they faced.

First, of course, they would have to pay for the collection of the clinical data FDA would require. The magnitude of this obligation would depend on a critical decision: Would FDA allow the banks to analyze the results of historical experience with allografts, or would it insist on new trials? A related issue was whether the banks could pool their results.¹³⁹ If FDA was prepared to allow them to rely on past experience and to pool their results, satisfying the Agency might not have seemed a daunting challenge.

The allograft processors were quickly disappointed, because FDA insisted that some prospective studies be undertaken, even under a jointly-sponsored investigational device exemption (IDE).¹⁴⁰ This decision meant that no bank could hope to secure approval of a PMA by the Agency's deadline. This in turn meant that any bank that wished to continue distribution after the deadline would have to live with the restrictions of any IDE that FDA was prepared to approve.¹⁴¹ Even if FDA was prepared to approve a large number of transplant surgeons as clinical investigators, it was likely that those sanctioned to conduct studies would represent only a subset of surgeons who had previously been implanting allograft valves.¹⁴²

Two other problems flowed from FDA's decision to require prospective studies. If some surgeons could not obtain allograft valves because they were not approved as investigators, they would have to find alternatives. Surgeons complained that, for juvenile patients, there were no good alternatives.¹⁴³ The problem could be

¹³⁷ Cardiovascular Devices; Extension of Effective Date of Requirement for Premarket Approval; Replacement Heart Valve Allograft, 56 Fed. Reg. 35,815 (July 29, 1991).

¹³⁸ *Id.*

¹³⁹ Cryolife was not interested in such an arrangement.

¹⁴⁰ *Regulation of Human Tissue Transplantation: Hearing on S. 2908 Before the Senate Committee on Labor and Human Resources*, 102nd Cong., 11 (Sept. 29, 1992) (statement of Michael Taylor, Deputy Commissioner for Policy, Food and Drug Administration).

¹⁴¹ *Id.*

¹⁴² STRONG ET AL., *supra* note 25, at 10.

¹⁴³ *Regulation of Human Tissue Transplantation: Hearing on S. 2908 Before the Senate Committee on Labor and Human Resources*, 102nd Cong., 26-27 (Sept. 29, 1992) (statement of Richard A.

ameliorated by adding surgeons to the roster of approved investigators, but this task proved more difficult than the processors or FDA anticipated. Cardiac surgeons are widely dispersed, and under FDA's regulations each implantation venue is considered a separate investigation site under a multi-site IDE.¹⁴⁴ FDA also requires that every site have an IRB willing to review the study protocol and assure that each patient's informed consent is obtained.¹⁴⁵ Thus adding a site required negotiations with the local IRB.

Ironically, the effort to convert unregulated distribution and use of allograft heart valves into what became a large, multi-site clinical study under an IDE created another problem, one that particularly affected pediatric patients with valve disease. Under the FDCA, shipment of a device for an approved clinical trial is for an "investigational" use.¹⁴⁶ For several years the Health Care Financing Administration (HCFA) equated "investigational" with "experimental," and refused to provide reimbursement for procedures that fell in the latter category.¹⁴⁷ Many private insurers mimicked the HCFA policy. By restricting distribution of allograft valves to approved "investigators": FDA converted what had been standard surgical practice into an experimental procedure—and thereby rendered many patients ineligible for reimbursement. This result triggered indignant letters from surgeons and from patients who learned they needed surgery for which they were not insured.¹⁴⁸ A year passed before FDA Commissioner Kessler was able to work out an agreement with HCFA under which that agency would no longer treat the "investigational" implantation of allograft valves as "experimental" surgery.¹⁴⁹

Hopkins, M.D., Director of Pediatric Cardiac Surgery, Georgetown University Medical Center).

¹⁴⁴ 21 C.F.R. pt. 812.35(b) (2002).

¹⁴⁵ 21 C.F.R. Part 56 (2002).

¹⁴⁶ 21 U.S.C. § 360(j)(g) (2001).

¹⁴⁷ See Sandy Rovner, *Insurers Balk at Paying for All Cancer Drugs*, WASH. POST, Oct. 31, 1989.

¹⁴⁸ *Regulation of Human Tissue Transplantation: Hearing on S. 2908 Before the Senate Committee on Labor and Human Resources*, 102nd Cong., 16 (Sept. 29, 1992) (statements of Randolph May, National Head of Tissue Services, American Red Cross); NTBC POSITION PAPER, *supra* note 26, at 28 (1991).

¹⁴⁹ "Dear Doctor" letter from Gordon Johnson, M.D., Director, Office of Health Affairs, Center for Devices and Radiological Health, Food and Drug Administration (Jun. 26, 1992) (on file with Houston Journal of Health Law & Policy); Letter from William Toby, Jr., Health Care Financing Administration, to David A. Kessler, M.D., Commissioner of Food and Drugs, Food and Drug Administration (May 22, 1992) (on file with Houston Journal of Health Law & Policy).

5. *The Valve Banks Go to Court*

After frustrating negotiations, six processors of allograft valves decided to challenge FDA's action in court. They faced an immediate jurisdictional puzzle. The time had long passed for seeking judicial review of FDA's 1987 rule under section 517(a)(4) of the FDCA.¹⁵⁰ The Agency's June 1991 announcement purported to interpret the earlier rule, not to constitute a new regulatory action, but it was only the recent announcement that appeared open to challenge. In addition, the banks were aware of cases holding that challenges to agency action that is a prelude to, or a product of, an action that by statute is reviewable in the courts of appeals must likewise be brought there.¹⁵¹ If the banks sued in district court, they risked being told they were in the wrong place; if they sought review in a court of appeals, they were certain to confront a government claim that they were too late.

Ultimately, the allograft processors decided to sue in *both* the Court of Appeals for the Seventh Circuit and the District Court for the Northern District of Illinois.¹⁵² They made similar claims in both courts. First, they contended that their valves were not subject to regulation as medical devices because Congress did not intend the Medical Device Amendments to apply to organs or tissues of human origin.¹⁵³ Notably, this claim did not persuade any court that ruled on it.¹⁵⁴ Yet it was a claim worth making because it dramatized the banks' main challenge to FDA's procedure. To the extent that no one in 1976 expected FDA to regulate human tissues as medical devices, the Agency's assertion in 1991 that human heart valves had been subject to regulation as early as 1980 could fairly be called surprising. If it were genuinely a surprise, the banks had a good argument that they had not been given notice of, much less an opportunity to comment on, the FDA's decision that they needed Agency approval to continue to distribute human heart valves.

¹⁵⁰ 21 U.S.C. § 335b(c) (2001).

¹⁵¹ *Telecomm. Research and Action Ctr. v. F.C.C.*, 750 F.2d 70 (D.C. Cir. 1984); *Indep. Bankers Ass'n of America v. Conover*, 603 F. Supp. 948 (D.D.C. 1985); *Cmty. Nutrition Inst. v. Young*, 773 F.2d 1356 (D.C. Cir. 1985); *Air Line Pilots Ass'n v. CAB*, 750 F.2d 81 (D.C. Cir. 1984).

¹⁵² *Alabama Tissue Ctr. of Univ. of Alabama Health Serv. Found., P.C. v. Sullivan*, 975 F.2d 373 (7th Cir. 1992) [hereinafter ATC 7th Circuit]; *Alabama Tissue Ctr. of Univ. of Alabama Health Serv. Found., P.C. v. Sullivan*, 1992 WL 162250 (N.D. Ill. July 7, 1992) [hereinafter ATC District Court I].

¹⁵³ ATC 7th Circuit, *supra* note 152, at 378.

¹⁵⁴ *Id.*

Moreover, the banks had a good argument that they had been prejudiced by FDA's unfair conduct. They had been deprived of the opportunity to persuade the Agency that it was wrong on the merits, i.e., that human heart valves should not be regulated as devices or, in any case, should not be in Class III. More importantly, their failure to learn until 1991 that they were subject to a rule issued in 1987 effectively deprived them of the 30 months the Act provided makers of Class III devices to prepare PMAs.¹⁵⁵

The allograft processors lost two rounds in court before they found a receptive audience. On September 16, 1992, the Seventh Circuit dismissed their petition for review of FDA's June 1991 announcement on the ground that it was not a rule that was subject to review in the courts of appeals.¹⁵⁶ The appeals court's dismissal implied that jurisdiction over any challenge to FDA's announcement must rest in district court. Prudently, the banks had sued there too, to guard against the very possibility that the court of appeals would decline jurisdiction.¹⁵⁷ But this precaution at first proved pointless because the district court treated the Seventh Circuit's dismissal as a ruling on the merits, which rendered the processors' claim moot.¹⁵⁸ Accordingly, the district court, too, dismissed the allograft processors' suit.¹⁵⁹

Only two of the original six plaintiffs appealed from the district court's refusal to entertain the processors' claims on the merits.¹⁶⁰ In its second encounter, the court of appeals finally grasped the thrust of the banks' complaint—and the source of their jurisdictional dilemma.¹⁶¹ The banks contended that they had not in 1986 understood, and could not have reasonably anticipated, that FDA's proposal to call for PMAs for "replacement heart valves"—or the final rule the Agency published a year later—would apply to heart valves recovered from human donors.¹⁶² As a consequence, they had no opportunity within the period specified by section 517(a)(4)

¹⁵⁵ 21 U.S.C. § 351(f)(2)(B) (2001).

¹⁵⁶ ATC 7th Circuit, *supra* note 152, at 379.

¹⁵⁷ ATC District Court I, *supra* note 152.

¹⁵⁸ *Alabama Tissue Ctr. of Univ. of Alabama Health Serv. Found., P.C. v. Sullivan*, 1992 WL 349646 (N.D. Ill. Nov. 16, 1992) [hereinafter ATC District Court II].

¹⁵⁹ *Id.* at 3.

¹⁶⁰ *Northwest Tissue Center v. Shalala*, 1 F.3d 522, 526-527 (7th Cir. 1993).

¹⁶¹ *Id.* (rehearing and suggestion for rehearing en banc denied Sept. 24, 1993).

¹⁶² *Id.* at 527.

to seek judicial review of FDA's 1987 rule.¹⁶³ More importantly, the remaining banks argued, FDA's June 1991 announcement that its rule did apply and that approved PMAs (or IDEs) were required no later than December 1991, effectively deprived them of the 30 months "grace period" that the Act guaranteed makers of all pre-Amendment Class III devices.¹⁶⁴ In the final analysis, their challenge was based on FDA's failure to provide notice of any proposal or decision to require PMAs for human heart valves.¹⁶⁵

So characterized, the court of appeals concluded, the allograft processors' challenge was not barred by its earlier ruling:

We believe plaintiffs may be "forgiven" for failing to file a timely challenge to the 1980 and 1987 regulations because the facts they allege indicate that they may not have received adequate notice of the effect of the regulations. . . .

We emphasize it is not the substance of the FDA's interpretation, but the manner in which it was announced that we believe merits review.

. . . Fundamental fairness requires that we ensure that the agency has not nullified the thirty-month grace period Congress provided to allow medical device manufacturers to comply with the amendments to the Act. . . .¹⁶⁶

Following several paragraphs expressing skepticism about the government's contention that the banks should have understood that regulations governing "replacement heart valves" could apply to them, the court concluded that "whether [FDA] provided adequate notice of its intention to regulate allografts is essentially a factual question . . . The district court is better equipped . . . to manage the gathering and presentation of evidence and to conduct the necessary factual inquiry."¹⁶⁷ Accordingly, it remanded the case for further proceedings.¹⁶⁸

¹⁶³ *Id.* at 528.

¹⁶⁴ *Id.* at 532.

¹⁶⁵ *Northwest Tissue Center*, 1 F.3d at 527.

¹⁶⁶ *Id.* at 530-32.

¹⁶⁷ *Id.* at 536.

¹⁶⁸ The Seventh Circuit's second opinion embodies, though never acknowledges, an internal inconsistency. It directed further proceedings in the district court which, if the tissue banks were correct about their lack of notice point, would lack jurisdiction. It would lack jurisdiction because, on the court of appeals' theory, the processors would have been entitled to challenge FDA's 1987 rule under section 517(a)(4) of the Act even though the statutory period for review had expired. 21 U.S.C. § 371(f)(1) (2001) Thus, the court of appeals was really asking the district court to conduct an inquiry whose purpose was to reveal whether it—the appeals court—still had jurisdiction under a provision that makes its jurisdiction exclusive.

This odd result is an artifact of the unusual nature of the allograft processors' claim, which tested the boundaries of the FDCA's conferral of limited jurisdiction on the

Following the Seventh Circuit's remand, further court proceedings were held in abeyance as the parties wrangled over possible settlement of the litigation. In December 1993, FDA promulgated new regulations governing the operations of all tissue banks.¹⁶⁹ Ten months later, FDA and the allograft processors announced that they had reached agreement,¹⁷⁰ and FDA soon announced the settlement in the *Federal Register*.¹⁷¹ Though some features of the settlement were puzzling, the most notable was FDA's willingness to resolve the dispute on terms that allowed the continued distribution of human heart valves without agency approval. FDA agreed that it would no longer enforce its 1991 requirement that human heart valves have PMAs "[but instead will] initiate procedures for the purpose of classifying these [medical] devices into 'Class II,' . . . with the simultaneous development and adoption of appropriate special controls."¹⁷²

Pending classification, which has not even now occurred, and the adoption of yet to be formulated special controls, FDA agreed that "allografts shall be subject only to the general controls applicable to all medical devices" under the Act.¹⁷³ These included the obligation to adhere to good manufacturing practices, as outlined in FDA's regulations.¹⁷⁴ The settlement agreement went on to define this obligation as satisfied by compliance with FDA's 1993 "interim

courts of appeals. If FDA's 1991 announcement were considered a new rule, jurisdiction over any challenge would clearly have rested in the court of appeals. Just as clearly, the rule would have been invalid because the Agency concededly had not provided notice of, or allowed comment on, its contents. If the 1991 announcement were merely an interpretation of the early 1987 rule, no court might have jurisdiction to hear a challenge to its validity. Suit in a court of appeals would be time-barred and no district court concededly had not provided notice of, or allowed comment on, its contents. If the 1991 announcement were merely an interpretation of the earlier 1987 rule, no court might have jurisdiction to hear a challenge to its validity. Suit in a court of appeals would be time-barred and no district court would have jurisdiction because court of appeals jurisdiction over any timely claim would be exclusive.

¹⁶⁹ Human Tissue Intended for Transplantation, 58 Fed. Reg. 65,514 (Dec. 14, 1993).

¹⁷⁰ *Northwest Tissue Center v. Shalala*, No. 91-C-6515 (N.D. Ill. Oct. 5, 1994) (stipulated order of dismissal), reprinted in *FDA Reclassifies Human Heart Valves as Class II Medical Devices*, AMERICAN ASS'N OF TISSUE BANKS INFO. ALERT, Oct. 11, 1994, at 2 [hereinafter NTC Dismissal Order].

¹⁷¹ Cardiovascular Devices; Notice of Agency Decision Not to Enforce Requirement of Premarket Approval; Replacement Heart Valve Allografts, 59 Fed. Reg. 52,078 (Oct. 14, 1994).

¹⁷² 59 Fed. Reg. at 52,078.

¹⁷³ NTC Dismissal Order, *supra* note 170.

¹⁷⁴ *Id.*

regulations" for banked human tissue and with AATB's "Standards for Tissue Banking."¹⁷⁵

E. FDA Initiates Comprehensive Regulation of Human Tissue

Several months earlier, in December 1993, FDA published general regulations governing human tissue intended for transplantation.¹⁷⁶ "To help prevent the transmission of AIDS and hepatitis through human tissue used in transplantation,"¹⁷⁷ the Agency mandated screening of tissue donors, testing of individual tissues for infectious disease, and maintenance of records to enable FDA inspectors to confirm compliance with the requirements for screening and testing.¹⁷⁸ Thus, in a single stroke, FDA asserted control over as many as 200 institutions whose activities had previously largely escaped federal regulation. FDA's action would have been provocative under any circumstances, but features were particularly controversial. The new regulations were promulgated without prior notice and were made effective immediately.¹⁷⁹ Tissue banks therefore were suddenly confronted with new legal obligations of which they had no prior notice, whose implementation depended on officials who had very little experience with tissue recovery or use.

1. FDA's Abrupt Decision to Regulate

FDA officials had previously been aware of the possibility that tissues could transmit infectious disease.¹⁸⁰ As noted earlier, the discovery in 1991 that a single donor had been the source of HIV infection in several recipients had spurred the Public Health Service to revise its guidance for collectors of tissues as well as blood and prompted FDA to declare that human heart valves were medical devices.¹⁸¹ By late 1993, FDA investigators had discovered practices among some tissue providers that caused great concern. At a Senate hearing in October, the Director of FDA's CBER recounted the Agency's findings:

¹⁷⁵ *Id.*

¹⁷⁶ Human Tissue Intended for Transplantation, 58 Fed. Reg. 65,514 (Dec. 14, 1993).

¹⁷⁷ 58 Fed. Reg. at 65,514.

¹⁷⁸ 58 Fed. Reg. at 65,517-18.

¹⁷⁹ 58 Fed. Reg. at 65,514.

¹⁸⁰ Nightingale, *supra* note 28, at 6.

¹⁸¹ Heart Valve Allograft Rule, *supra* note 65.

[S]everal tissue bank directors have been solicited by individuals offering to sell tissue that originates from other countries. Generally, these contacts have been unwilling to declare the actual source of the tissue, to provide the documentation as to the cause of death, the medical records of the donor, the results of donor screening and testing, or to furnish samples of donor serum for testing.¹⁸²

At the same hearing, the manager of the Northwest Tissue Center in Seattle said she had "received calls from brokers offering to send us tissue for processing from Russia, Eastern Europe, and Central and South America."¹⁸³ She endorsed the imposition of "very strict controls . . . to ensure the same standards [as are followed by domestic tissue banks] . . . because of the potential of unknown diseases that might be transmitted."¹⁸⁴

In the preamble to its regulations, FDA summarized the results of its own investigations:

In a relatively brief period of time, the agency was able to ascertain, in a few isolated instances, the availability for important and distribution, of tissue materials that do not meet minimal screening standards for transmission of infectious disease. . . . Two persons indicated immediate willingness to import tissues within weeks from donors from whom full medical histories and proper donor screening and testing had not been obtained. . . . Furthermore, the circumstances of alleged donation offered to agency investigators, without consent or notice to concerned relatives, would have precluded adequate evaluation of the donor's risk factors that would be relevant to minimize the potential for infectious disease transmission. . . .

One purveyor provided agency investigators with blood samples from a prospective donor-cadaver accompanied by documentation of previous infectious disease testing, including alleged testing for hepatitis B. On retesting by the Government, the sample was confirmed to be markedly positive for hepatitis B surface antigen. . . . The agency currently believes that these instances do not represent the predominant practice within the industry. Nonetheless, the traffic in tissue for transplantation without adequate testing or donor screening, whether domestic or imported, cannot be permitted to occur.¹⁸⁵

This account formed the basis for FDA's determinations that providing notice and opportunity for comment was "contrary to the public interest," under section 553(b)(B) of the APA, and that it had "good cause," under section 553(d)(3), to make its regulations effec-

¹⁸² *Regulation of Human Tissue Banks: Hearing Before the Subcommittee on Regulation, Business Opportunities, and Technology, 103d Cong, 1st Sess. 56 (1993)* (statement by Kathryn Zoon, Ph.D.) [hereinafter 1993 Tissue Bank Hearing].

¹⁸³ *Id.* at 194 (statement by Dr. Moogk).

¹⁸⁴ *Id.*

¹⁸⁵ Human Tissue Intended for Transplantation, 58 Fed. Reg. 65,514, 65,516 (Dec. 14, 1993).

tive immediately.¹⁸⁶ The Agency did, however, invite comments on the new "interim" regulations.¹⁸⁷ FDA's decision to bypass the APA's rulemaking procedures was never challenged in court, but the American Association of Tissue Banks (AATB) expressed disappointment that FDA found it necessary to implement new restrictions without affording any opportunity to question their contents.¹⁸⁸ At the same time, AATB and most other commenters supported the substance of FDA's requirements.¹⁸⁹

2. Coverage and Authority of FDA's "Interim" Regulations

Describing "human tissue" as lacking "direct or active Federal oversight,"¹⁹⁰ FDA defined the category as including "musculoskeletal and integumentary materials that may be recovered from living or cadaveric donors," which "largely consist of bone, ligaments, tendons, fascia, cartilage, corneas, and skin" used in disease treatment or reconstructive surgery.¹⁹¹ The new regulations did not apply to "tissues already regulated . . . as drugs, biological products, or medical devices,"¹⁹² or to vascularized organs and bone marrow (overseen by other parts of the Public Health Service) and human milk.¹⁹³ Significantly, FDA also specifically excluded "semen [and] other reproductive tissue," without identifying any other federal agency with oversight authority.¹⁹⁴

From the outset a critical issue for tissue banks was whether processing that altered the appearance or form, or facilitated the use, of a tissue would cause it to fall outside the coverage of the new regulations—and under the more stringent requirements for drugs or medical devices. FDA's treatment of this issue was not altogether reassuring. The Agency stated that its regulations applied to

¹⁸⁶ 5 U.S.C. §§ 553(b)(B), 553(d)(3) (2002); Human Tissue Intended for Transplantation, 58 Fed. Reg. at 65,518.

¹⁸⁷ 58 Fed. Reg. at 65,518.

¹⁸⁸ Human Tissue Intended for Transplantation, 62 Fed. Reg. 40,429, 40,440 (July 29, 1997) (to be codified at 21 C.F.R. pts. 16 and 1270); Jonathan Kahan, *FDA Regulation of Tissue and Cellular Products: Avoiding Overregulation While Protecting Public Health*, RA FOCUS, 6 (1997); AATB Comments, *supra* note 67, at 6-7.

¹⁸⁹ Human Tissue Intended for Transplantation, 62 Fed. Reg. at 40,429.

¹⁹⁰ Human Tissue Intended for Transplantation, 58 Fed. Reg. 65,514 (Dec. 14, 1993).

¹⁹¹ 58 Fed. Reg. at 65,514.

¹⁹² 58 Fed. Reg. at 65,516.

¹⁹³ 58 Fed. Reg. at 65,516.

¹⁹⁴ 58 Fed. Reg. at 65,516.

tissue processed or stored "by methods not intended to change tissue structure or functional characteristics."¹⁹⁵ "Tissues that are processed or stored only in ways to prevent transmission of infectious disease and to preserve clinical usefulness would be covered by the regulation."¹⁹⁶ This explanation left something to the imagination. Most of the processes tissue banks employed were intended either to eradicate infectivity or enhance clinical utility, but if the word "preserve" meant "kept unchanged," the Agency's language implied that technological innovation carried risks.

Perhaps the most significant feature of FDA's "interim" regulations was its decision not to rely on the FDCA for legal authority. Instead, the Agency invoked Section 361 of the Public Health Service Act, an old provision of awesome breadth.¹⁹⁷ In its current form, Section 361 reads:

The Surgeon General [i.e., FDA]. . . is authorized to make and enforce such regulations as in his 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. For purposes of carrying out and enforcing such regulations, the Surgeon General may provide for such inspection fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in his judgment may be necessary.¹⁹⁸

FDA offered several reasons for its reliance on Section 361. The most important was the most obvious; the provision is aimed at the very sort of problem that prompted the Agency to act, the risk that tissue transplants could transmit hepatitis or HIV. FDA did not, however, address two consequences of relying on Section 361. First, the provision only confers authority to prevent the transmission of disease.¹⁹⁹ The more important consequence is a product of the section's brevity. Unlike the FDCA, which prescribes rather specific requirements for each of the categories of products that it covers, Section 361 speaks in expansive terms about the kinds of

¹⁹⁵ Human Tissue Intended for Transplantation, 58 Fed. Reg. at 65,516-17.

¹⁹⁶ 58 Fed. Reg. at 65,516.

¹⁹⁷ 58 Fed. Reg. at 65,516.

¹⁹⁸ 42 U.S.C. § 264(a) (2001).

¹⁹⁹ This does not necessarily mean that FDA could not regulate a bank whose tissue was recovered and used within a single state, but presumably the Agency would have to show that regulation of such local activity was calculated to help combat the interstate movement of disease. See *Public Citizen v. Heckler*, 653 F. Supp. 1229 (D.D.C. 1986) (imposing a ban on interstate shipment of unpasteurized milk).

measures FDA may adopt. The objective of regulation is circumscribed; the means are unlimited. Had FDA opted to rely on the FDCA, e.g., by declaring all tissue implants to be medical devices, it would have automatically triggered a series of requirements applicable to all medical devices. By relying solely on Section 361, FDA retained discretion to fashion the requirements it concluded were sufficient for the task.

3. FDA's Implementation of its "Interim" Regulations

The regulations specifically provided that organizations engaged in the recovery, processing, or distribution of human tissues would be subject to FDA inspection—as are manufacturers and distributors of other regulated products.²⁰⁰ They also authorized agency officials to order the recall and/or destruction of tissue “when there is a significant question as to the source of the tissue, the adequacy of the testing of the tissue, or the adequacy of donor selection.”²⁰¹ While taken at face value, this language could expose banks to disputes over the “adequacy” of their testing or screening, elsewhere the Agency narrowed this authority to “human tissue that has been collected or distributed in violation of the regulations.”²⁰²

It was inevitable that tissue banks would initially find visits by FDA inspectors disconcerting. Most had no prior experience with FDA or its field personnel. Several later complained about the conduct of agency inspectors, but to the experienced ear these complaints do not suggest that inspectors were behaving in unusually intrusive ways.²⁰³ One frequent complaint was that FDA inspectors issued “citations” for practices that were not specifically forbidden by the regulations.²⁰⁴

These complaints reflected unfamiliarity with FDA's routine inspectional practices. At the conclusion of an inspection the inspector customarily prepares, and provides to the establishment, a

²⁰⁰ Human Tissue Intended for Transplantation, 58 Fed. Reg. 65,514, 65,517-65,518 (Dec. 14, 1993).

²⁰¹ 58 Fed. Reg. at 65,518.

²⁰² Note that FDA does not possess general statutory recall authority. The Device Amendments do permit FDA to order recalls, but provisions governing drugs and foods are silent on the point. 58 Fed. Reg. at 65,518.

²⁰³ See Kahan, *supra* note 35 at 5.

²⁰⁴ See Letter from AATB to FDA, at 5 (March 14, 1994) [hereinafter 1994 AATB Letter] (on file with author) (stating “many feared unannounced and immediate inspections followed by summarily imposed sanctions for non-compliance.”).

list of inspectional observations, titled a Form 483.²⁰⁵ This is a summary of conditions or practices that the inspector believes should be called to the attention of the establishment as well as reported to his/her supervisors.²⁰⁶ Only if the inspector's superiors agree that the conditions described indicate violations, however, will the establishment receive another communication from FDA.²⁰⁷ (This communication will usually take the form of a warning letter or, less commonly, initiation of formal enforcement action). A Form 483, therefore, can be the prelude to further action, but it has no independent legal significance. Firms that have experience with FDA inspections understand this.

Tissue banks found it difficult to be so sanguine, however. Inexperienced bank personnel have been slow to grasp that the entries in a Form 483 do not represent formal charges of legal violations. FDA's own explanation of the circumstances in which tissue banks would receive a Form 483 left something to the imagination: “[I]f potential significant violations of the regulations are found, the FDA investigator will issue . . . a list of “Inspectional Observations,” which will describe the observations of the investigator that may represent violations of the regulations.”²⁰⁸ The first clause suggests a bank will be given a Form 483 only if the inspection uncovers “significant violations.” Thus, if, following an inspection, a tissue bank receives a form listing “inspectional observations,” it might reasonably assume that the conditions described there are considered “violations” of a significant sort.

A second reason tissue banks were distressed by FDA's practice is shared by other firms subject to FDA inspection. Under FDA's Freedom of Information Act regulations, a Form 483 is a publicly available document as soon as it is handed to the establishment; the Agency will provide a copy up on request to any member

²⁰⁵ Dep't of Health and Human Servs., Food & Drug Admin., Tissue Reference Group Progress Workshop 53 (2001), available at <http://www.fda.gov/cber/minutes/tisprog082901.pdf>.

²⁰⁶ *Id.*

²⁰⁷ Human Tissue Intended for Transplantation, 62 Fed. Reg. 40,429, 40,439 (Jul. 29, 1997) (to be codified at 21 C.F.R. pts. 16 and 1270); Peter Barton Hutt, *Public Information and Public Participation in the Food & Drug Administration*, 36 Q. BULL. OF THE ASS'N OF FOOD AND DRUG OFFICIALS 212 (1972), reprinted in PETER HUTT & RICHARD MERRILL, *FOOD AND DRUG LAW* 1300 (2d ed. 1991); Anthony C. Celeste, *The Inevitable FDA Inspection*, 34 FOOD DRUG COSM. L.J. 32, 37-39 (1979); PHS Workgroup on Organ and Tissue Transplantation, *Tissue and Organ Transplantation Assessment Report* 9-10 (Jul. 18, 1991).

²⁰⁸ Human Tissue Intended for Transplantation, 58 Fed. Reg. 65,514, 65,518 (Dec. 14, 1993).

of the press or public.²⁰⁹ Consequently, a Form 483 can receive wide publicity before the recipient bank has had an opportunity to respond, even to FDA. Moreover, even if the establishment has provided a response, the FDA feels under no obligation to supply a copy to persons who request the Form 483. The form bears no legend describing its preliminary character or alerting the reader that a response may be forthcoming or already on file.

A more serious source of controversy stemmed from FDA's declaration, in its preamble: "This interim rule is effective immediately for tissues currently in storage."²¹⁰ This meant, according to FDA, that tissues in inventory "must either be immediately quarantined or have available the required documentation of donor testing and screening."²¹¹ Although the Agency invited comment on the "feasibility and burdensomeness" of this determination, inspectors sometimes proceeded to act as though it were effective immediately.²¹² As a consequence, many tissues that had already been collected, processed, and in some instances shipped to another bank before issuance of the "interim" regulations were vulnerable to orders to destroy.

FDA's decision to apply its regulations to tissues already in inventory gave rise to two sorts of disputes. One, of less immediate concern, involves the arguable conflict between the Agency's expectation of a next-of-kin inquiry about the health and habits of a donor, and state laws that "presume consent" for eye donation.²¹³ The second stems from the inevitable imprecision of regulations that were adopted without opportunity for comment and that purport to rely heavily on the standards of voluntary private organizations. This imprecision gave the regulations a plasticity that allowed them to take on new meaning with the passage of time. An example will illustrate.

FDA's regulations required that a tissue bank must have had access to, and recorded, sufficient information about a donor's health history to provide reasonable assurance that he or she did not

²⁰⁹ 21 C.F.R. § 20.101(a) (2002).

²¹⁰ Human Tissue Intended for Transplantation, 58 Fed. Reg. 65,514, 65,517 (Dec. 14, 1993).

²¹¹ 58 Fed. Reg. at 65,517.

²¹² Human Tissue Intended for Transplantation, 58 Fed. Reg. at 65,514; Human Tissue Intended for Transplantation, 62 Fed. Reg. 40,429 (July 29, 1997); AATB Comments, *supra* note 67, at 13-14.

²¹³ Human Tissue Intended for Transplantation, 62 Fed. Reg. at 40,437; AATB Comments, *supra* note 67, at 11.

have a transmissible disease at the time of death.²¹⁴ The regulations did not say specifically what information is essential. The Agency's preamble adverts to the AATB standards, but these do not prescribe every detail of the necessary information either. In January 1995, FDA issued "guidance" to its inspectors of tissue banks.²¹⁵ This guidance emphasized the importance of discovering whether a donor had undergone any form of body piercing, had been tattooed or had an ear lobe or nostril pierced, and whether he or she had displayed discolored stool near the time of death.²¹⁶ Evidence of body piercing could suggest a higher risk of HIV infection; stool coloration could be a symptom of hepatitis.²¹⁷

Not surprisingly, many tissue banks discovered that they lacked this suddenly-critical information for much of their inventory.²¹⁸ To seek the necessary information weeks or months after donation, from family members whose views about the donor's death or the wisdom of donation could have changed, would at the very least be a sensitive undertaking. But this apparently was what some FDA inspectors believed tissue banks were obligated to do, or face ultimate destruction of tissues in inventory.

This example illustrates that "retroactivity" can have multiple meanings. FDA officials apparently concluded that they could not sound the alarm about the risks of disease transmission and prescribe future precautions to assure that tissues are disease free, and at the same time ignore the circumstances under which already collected tissue had been recovered. If the risk of disease transmission was as serious as the Agency claimed, it could hardly allow inventories to clear the market without knowing what steps had been taken to screen and test the donors. But FDA threatened "retroactive" regulation of a more subtle sort. In attempting to give meaning to the requirement for donor screening, FDA expected information that few tissue banks were likely to possess about their donors—because

²¹⁴ Human Tissue Intended for Transplantation, 58 Fed. Reg. 65,514, 65,517 (Dec. 14, 1993).

²¹⁵ *Guidance Concerning Application of Testing and High Risk Criteria for HIV and Hepatitis for Banked Human Tissue* (Jan. 26, 1995) [hereinafter *Testing Guidance*].

²¹⁶ *Id.* at 2; Comments from American Association of Tissue Banks to Dockets Management Branch of Food and Drug Administration 4 (July 19, 1995).

²¹⁷ *Testing Guidance*, *supra* note 215, at 2; Comments from American Association of Tissue Banks to Dockets Management Branch of Food and Drug Administration 4 (July 19, 1995).

²¹⁸ See Letter from James C. Simmons, Acting Director, Office of Compliance, Center for Biologics Evaluation and Research, Food and Drug Administration, to Ted Eastlund, M.D., President of American Association of Tissue Banks (Feb. 16, 1995) (on file with Houston Journal of Health Law & Policy).

it had not previously been recommended by public health authorities.

4. *Biodynamics Litigation*

In March 1995, a decision by FDA inspectors in Baltimore, later endorsed by CBER compliance officials, triggered a law suit that threatened the regulatory edifice the Agency had only recently erected. The dispute began with FDA's detention of several lots of dura mater that Biodynamics, Inc., sought to import from Germany.²¹⁹ The tissues had been recovered from donors in Florida by Florida banks²²⁰ and then been shipped to Germany for processing.²²¹ FDA challenged their reimportation on the ground that they lacked the documentation of donor screening that the Agency's guidance said was required.²²² The correctness of FDA's claim or of Biodynamics' response that the tissues had been procured in accordance with AATB standards, need not detain us. Of immediate interest is the hearing before U.S. District Judge Fred Motz that shortly followed.²²³ After its efforts to secure the release of the tissues failed, Biodynamics filed suit against FDA, seeking an injunction and challenging what it claimed was the Agency's practice of treating its guidance to inspectors as binding on tissue banks. Biodynamics later considered adding a claim that FDA's underlying regulations had been adopted in violation of the APA.²²⁴

The dispute centered on the adequacy of the records documenting the screening of donors of Biodynamics' dura mater. Apparently it was the view of FDA's inspectors that the tissues lacked the documentation required by section 1270.33(d) of the "interim" regulations.²²⁵ In particular, the records did not reveal whether any attempt had been made to determine whether the donors had undergone body piercing or had displayed symptoms suggestive of

²¹⁹ See Kahan, *supra* note 35, at 3.

²²⁰ Transcript of Temporary Restraining Order Hearing Before the Honorable J. Frederick Motz, United States District Court Judge at 5, 89, *Biodynamics Int'l, Inc. v. United States of America*, No. JFM-95-919 (D. Md. 1995) [hereinafter *Biodynamics Hearing Transcript*].

²²¹ *FDA Orders Detainment of Two Shipments of Bone Allografts*, MEDICAL INDUSTRY TODAY, March 20, 1995, at DEVICE & DIAGNOSTICS.

²²² See *id.*

²²³ *Biodynamics Hearing Transcript*, *supra* note 220.

²²⁴ See *id.* at 29.

²²⁵ 21 C.F.R. 1270.33(d) (2002); *Biodynamics Hearing Transcript*, *supra* note 220, at 24.

hepatitis.²²⁶ Biodynamics had no good answers to the FDA charges. Records compiled at the time of recovery contained a good deal of information about the health of the donors but did not reveal whether questions that FDA claimed should have been asked were in fact put to the donors' next of kin.²²⁷ Biodynamics contested FDA's position on other grounds. From the company's perspective, the Agency appeared to be relying on requirements that (a) were not spelled out in the "interim" regulations, (b) were not binding because they had not been promulgated as rules, (c) had not been made public, and (d) were being applied to tissue recovered months before the guidance was distributed.²²⁸ Biodynamics also claimed, without denial, that tissues from many of the same donors had been processed domestically and distributed with the knowledge of FDA's office in Tampa.²²⁹

Biodynamics found a sympathetic audience in Judge Motz. The hearing on its motion for a preliminary injunction exposed several fault lines in the Agency's position which, at bottom, seems to have been this: The "interim" regulations required that tissues be accompanied by records demonstrating that the donors were adequately tested and screened to guard against the possibility that they were infected.²³⁰ The regulations themselves were clearly binding—assuming that FDA had been justified in invoking the exception in section 553(c) of the APA.²³¹ The Agency's guidance represented a reasonable articulation of what the regulations' requirement of "adequate" screening entailed.²³²

This theory of FDA's case was never satisfactorily explained to Judge Motz. Even if it had been, however, FDA would have confronted difficulties at least as great as those he identified. For example, Judge Motz expressed doubt that the Agency had any basis for issuing its interim regulations without opportunity for comment,²³³ pointing out that Commissioner Kessler at the time had gone out of his way to assure the public that no emergency was presented by

²²⁶ See *id.* at 65.

²²⁷ *Id.* at 24.

²²⁸ *Id.* at 17; *Biodynamics International, Inc. Announces Detention Order*, PR NEWSWIRE, March 17, 1995.

²²⁹ *Biodynamics Hearing Transcript*, *supra* note 220, at 20.

²³⁰ *Id.* at 24.

²³¹ *Id.* at 28.

²³² 21 C.F.R. § 1270.21 (2002).

²³³ See *Biodynamics Hearing Transcript*, *supra* note 220, at 139.

prevailing practices in the recovery, processing, or use of human tissue.²³⁴

But Judge Motz reserved his sharpest criticism for the government's contention that it could rely on FDA's guidance as a basis for detaining Biodynamics tissue.

This isn't an interpretative guideline. It's not just telling an inspector the kinds of things to look at to see if it's adequate. It's basically saying if you don't ask this question in this way we're going to quarantine your product if we decide that you are somebody we want to go after And you do this on the basis of guidelines. . . . And you do it retroactively. [T]hat's not American.²³⁵

Judge Motz rejected the argument that the guidance constituted a valid interpretive rule.²³⁶ He pointed out that FDA had never made the guidance public, much less published it in the Federal Register.²³⁷

At the conclusion of what must have been a chastening experience for the FDA officials present, Judge Motz granted Biodynamics' motion for a preliminary injunction and indicated that he was prepared to grant a permanent injunction if one were sought.²³⁸ And, he suggested that he would be receptive to a broader challenge to FDA's interim regulations.²³⁹

. . . There certainly is a substantial question as to whether or not the adoption of the "interim rule" by emergency measure was appropriate. . . . I have grave doubts as to whether or not any emergency existed. . . . But it occurs to me as a practical matter the emergency that did exist, if there was one, related to tissue provided by foreign donors. . . .

In any event, around this time . . . the head of the FDA is saying there is no emergency. . . .

. . . And if there was, there certainly should have been quicker follow-up in terms of the public hearing on the propriety of the rule. And instead there was distribution of secret guidelines to the inspectors. . . . I can find myself getting riled up when essentially having avoided public comment, the government agents then submitted "guidances" . . . let's just say guidances in this case somewhat euphemistically, when the guidances are absolutely dispositive of a company's life, depending upon the whim of a government agent as to whether that's a company that the government chooses to go after. This is not interpretative in any sense.

²³⁴ See *id.* at 9, 138-140.

²³⁵ *Id.* at 133.

²³⁶ See *id.* at 139.

²³⁷ *Id.* at 17.

²³⁸ Biodynamics Hearing Transcript, *supra* note 220, at 133.

²³⁹ See *id.* at 148.

. . . And it just isn't fair to retroactively through secret guides issued to inspectors to say, well, now we're saying that these are the questions which we say have to have been asked. That's not interpretation because the creation of a regulation with absolute substantive enactments is not right. It absolutely undermines the APA and in my view, is not to be tolerated. . . .

. . . So when we have a circumvention of the APA as I find that occurred in this case, that to me is an independent public which warrants granting the relief that the plaintiff asks.²⁴⁰

Judge Motz declined the Government's request to stay his order pending an appeal,²⁴¹ and two days later the Fourth Circuit rejected the government's request for a stay.²⁴² There then ensued several weeks of negotiations between Biodynamics and FDA in an attempt to work out terms on which the Agency would permit importation of tissue lots processed in Germany and the company would provide more complete documentation of the condition of its donors and the inquiries made about their habits and health.²⁴³

5. FDA Augments Its System

When FDA promulgated the interim regulations in December 1993, it predicted that it would respond to comments before the end of the summer of 1994.²⁴⁴ In the event, over three years elapsed before the Agency completed the first stage of construction of a comprehensive regulatory system for tissue.²⁴⁵ There were several reasons for this delay.

First, the 1994 elections produced a Congress that was much less sympathetic to health regulation than predecessors. Shortly after the election House Speaker Gingrich described FDA as "the greatest job-killer in America."²⁴⁶ Several new members vowed to introduce legislation to "reform" FDA's regulation of medical products, and trade associations leapt at the opportunity to push "re-

²⁴⁰ *Id.* at 137-41, 144.

²⁴¹ *Id.* at 149.

²⁴² See *Biodynamics Gets Preliminary Injunction Against FDA*, MEDICAL INDUSTRY TODAY, April 19, 1995, at DEVICE & DIAGNOSTICS.

²⁴³ See *Biodynamics Int'l, Inc. v. United States of America*, No. JFM-95-919 (D. Md. 1995) (order dismissing case); *FDA, Biodynamics Resolve Allograft Flap*, MEDICAL INDUSTRY TODAY, September 28, 1995, at DEVICE & DIAGNOSTICS.

²⁴⁴ See *Human Tissue Intended for Transplantation*, 58 Fed. Reg. 65,514, 65,516 (Dec. 14, 1993).

²⁴⁵ See *Human Tissue Intended for Transplantation*, 62 Fed. Reg. 40,429 (July 29, 1997) (the final rule was published in the Federal register in July 1997).

²⁴⁶ John Schwartz, *Conservative Foes of Government Regulation Focus on the FDA*, WASH. POST, Jan. 21, 1995, at A7.

form" proposals of their own.²⁴⁷ Congressional oversight hearings probed FDA's reputed tardiness in approving new drugs and devices.²⁴⁸

The shift in control of the Congress placed FDA on the defensive for the first time in several years. With the exception of its ill-fated plan to regulate cigarettes, FDA did not advance any major regulatory initiatives for over a year. The replacement of Democratic committee chairs in the House and Senate derailed legislation that would have confirmed FDA's authority to regulate human tissue. The possibility that Congress might provide the Agency with additional resources in the form of "user fees" disappeared. Thus, Agency officials must have come to believe that implementation of any new requirements, not to mention those imposed by the interim regulations, would have to be funded out of current resources.²⁴⁹

In the wake of Judge Motz's ruling, FDA announced the availability of a new version of its guidance for inspectors of tissue banks.²⁵⁰ The document itself reflected rather modest changes in the March version, which had triggered the Agency's detention of Biodynamics' tissue.²⁵¹ More significant was the Agency's decision to invite comments before the new guidance was distributed to its field inspectors.²⁵²

F. FDA Embellishes its Tissue Program

The interim regulations that FDA promulgated in December 1993 proved to be just the first installment in the Agency's development of an elaborate program for regulating human tissue and "tis-

²⁴⁷ See, e.g., Kathleen Day, *Drug, Biotech Industries Cautious on FDA Reform; Many See Business Benefits in Oversight*, WASH. POST, May 20, 1995, at D1.

²⁴⁸ See, e.g., *Technology Development: Hearing Before the House Comm. On Science* (1995) (statement of Dan Garner, Ph.D., on Behalf of Cellmark Diagnostics and Zeneca, Inc.), available at 1995 WL 10731951.

²⁴⁹ See *Human Tissue Intended for Transplantation*, 58 Fed. Reg. 65,514, 65,519 (Dec 14, 1993).

²⁵⁰ *Under Court Pressure, FDA Releases New Policy on Donor Tissue*, FDA WEEK, July 7, 1995, at 13, 14; Comments from American Association of Tissue Banks to Dockets Management Branch of Food and Drug Administration 1 (July 19, 1995).

²⁵¹ *Id.* at 14-15.

²⁵² See *Human Tissue Intended for Transplantation*, 58 Fed. Reg. 65,514, 65,516, 65,519 (Dec. 14, 1993).

sue-based products."²⁵³ FDA has expanded the basic structure created by these "interim" regulations in subsequent proceedings.²⁵⁴

1. FDA Envisions a New Regime

In July 1997 FDA concluded the proceeding it began nearly four years earlier by promulgating final regulations governing distributors of human tissues for transplantation.²⁵⁵ The final regulations closely resembled the so-called "interim rule." Tissue banks were required to assure that tissue donors were screened for disease;²⁵⁶ individual tissues were required to be tested;²⁵⁷ and records were required to confirm screening and testing and document the distribution of tissue so that banks could recall tissues whose safety was later called into question.²⁵⁸ The preamble to the final regulations addressed most of the sometimes caustic comments filed in response to the "interim rule."²⁵⁹

More significantly FDA had, several months earlier, released for discussion an unusual document, titled "A Proposed Approach to the Regulation of Cellular and Tissue-Based Products."²⁶⁰ This document, whose availability was announced in the *Federal Register*²⁶¹ but whose text never appeared there, reflected extensive discussions within the Agency. In it FDA said that it expected to confront a variety of new technologies that relied on or sought to manipulate human tissue for therapeutic ends.²⁶² Of these, conventional tissue transplants presented the fewest regulatory challenges. Their surgical uses were well known and their recovery and

²⁵³ See *id.* at 65,514.

²⁵⁴ *Human Tissue Intended for Transplantation*, 62 Fed. Reg. 40,429 (July 29, 1997). The final rule required testing facilities to ensure that specific minimum screenings for infectious disease were performed, that medical records be made available for FDA inspection, contained inspection provisions for the facilities and contained procedures for destruction of tissue for which no documentation is available. 62 Fed. Reg. at 40,429.

²⁵⁵ *Human Tissue Intended for Transplantation*, 62 Fed. Reg. 40,429 (July 29, 1997).

²⁵⁶ 21 C.F.R. §§ 1270.21(d), (e) (2002).

²⁵⁷ 21 C.F.R. at §§ 1270.21(a), (b) (2002).

²⁵⁸ 21 C.F.R. at §§ 1270.33(d), 1270.35(c) (2002).

²⁵⁹ See *Human Tissue Intended for Transplantation*, 62 Fed. Reg. 40,429, 40,432 (July 29, 1997).

²⁶⁰ FOOD & DRUG ADMIN., A PROPOSED APPROACH TO THE REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS. THE FOOD AND DRUG ADMINISTRATION (1997) [hereinafter Proposed Approach].

²⁶¹ Proposed Approach to Regulation of Cellular and Tissue-Based Products; Availability and Public Meeting, 62 Fed. Reg. 9,721 (Mar. 4, 1997).

²⁶² Proposed Approach, *supra* note 260, at 5-6.

processing were, by now, subject to regulatory oversight. However, the Agency anticipated more exotic technologies that would involve more invasive procedures or more complex manipulations of human source material for which screening of donors, testing of tissues, and record-keeping—the core elements of its soon-to-be final tissue regulations—would not assure safety or clinical performance.²⁶³

FDA's plan set forth the Agency's thinking about a critical issue: When should a tissue-based product require premarketing proof of safety and effectiveness?²⁶⁴ In other words, when should a product be regulated as a new drug or Class III medical device? In a real sense this restated the issue FDA confronted several years earlier when it announced that allograft heart valves were required to have effective PMAs.²⁶⁵ The Agency's later retreat from this position in the specific case did not mean that it had abandoned the view that some "tissue-based products" should be (and under the law could be) regulated as drugs or devices. FDA's plan, however, did not attempt to resolve this question for any particular technology; its aim was at once more ambitious and less controversial.

The plan's ambition lay, first, in its assertion that some tissue-based products should be regulated under the FDCA, and, second, in its attempt to enunciate criteria for determining when a particular technology should be so regulated.²⁶⁶ Essentially, FDA embraced the principle of familiarity. If a donated tissue was expected to perform in the recipient the same function it performed in the donor, its effectiveness could be assumed and its safety could be assured if appropriate screening and testing were conducted.²⁶⁷ In an effort to capture this concept, the Agency said it would ask whether a tissue had been more than "minimally manipulated" and whether it was intended for other than a "homologous use."²⁶⁸ Significant changes in the form of a tissue or implantation in a different part of the body to perform a novel function would, the Agency suggested, undermine the presumption of clinical utility and safety.²⁶⁹ FDA recognized that there would be disputes about whether a particular tissue

²⁶³ *Id.* at 18-19.

²⁶⁴ *See id.* at 6.

²⁶⁵ Heart Valve Allograft Rule, *supra* note 65.

²⁶⁶ *See* Proposed Approach, *supra* note 260, at 6, 12-17.

²⁶⁷ *See id.* at 15.

²⁶⁸ *See id.* at 11.

²⁶⁹ *See id.* at 13-15, 15-16.

had previously been altered too much or would be used in too novel a way, and it reminded readers that it had previously established an internal tribunal, known as the Tissue Reference Troup, (TRG), to resolve such issues.²⁷⁰ The plan did not describe the procedures of the TRG, however, or address the question of how its decisions would be implemented.

From the perspective of most tissue banks, the FDA plan contained both good news and bad. The good news lay in FDA's acknowledgment that most tissues currently in surgical use would continue to be regulated under the "interim rule" (or its soon-to-appear final version) and would not be required to undergo agency marketing approval—as drugs or as medical devices.²⁷¹

A few months later, FDA promulgated its final regulations for processors of conventional tissues, described above.²⁷² It then set about developing what CBER Director Dr. Kathryn Zoon later labeled its "Tissue Action Plan," which defined the additional measures required to complete a comprehensive scheme for regulating human tissue.²⁷³

2. Components of FDA's Tissue Action Plan

Since 1997, FDA has proposed or adopted regulations elaborating three basic obligations of tissue banks. First, the Agency proposed, and later made final, regulations that require distributors of human tissue to register with FDA and submit annually a listing of their products.²⁷⁴ As authority for these uncontroversial requirements, FDA relied on two statutory provisions. For organizations distributing tissues already regulated as medical devices, the

²⁷⁰ *Human Tissue Banking: Hearing Before the Senate Subcommittee on Investigations, Committee on Government Affairs*, 107th Cong. (May 24, 2001) (Statement of Kathryn C. Zoon, Ph.D. Director, Center for Biologics Evaluation and Research, Food and Drug Administration) at <http://www.fda.gov/ola/2001/humantissue.html> (last visited May 30, 2002).

²⁷¹ Proposed Approach, *supra* note 260, at Table 1.

²⁷² Human Tissue Intended for Transplantation, 62 Fed. Reg. 40,429 (July 29, 1997).

²⁷³ *Human Tissue Banking: Hearings Before the Senate Subcommittee on Investigations, Committee on Government Affairs*, 107th Cong. (May 24, 2001) (Statement of Kathryn C. Zoon, Ph.D. Director, Center for Biologics Evaluation and Research, Food and Drug Administration) at <http://www.fda.gov/ola/2001/humantissue.html> (last visited May 30, 2002).

²⁷⁴ Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products, 63 Fed. Reg. 26,744 (May 14, 1998) (proposed rule). Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5,447 (Jan. 19, 2001).

Agency invoked section 510 of the FDCA.²⁷⁵ For banks whose products consisted entirely of so-called conventional tissues—tissues regulated under the final version of the 1993 “interim rule”—FDA relied on Section 361 of the Public Service Act.²⁷⁶ The Agency’s argument—that official knowledge of the identity and location of organizations that distribute tissue and of the tissues they distribute would aid in preventing disease—was not challenged by any of the comments on the Agency’s proposal.

FDA next proposed significant revisions to its existing requirements for screening donors of tissue.²⁷⁷ These were not uncontroversial, however, and three years later had not been promulgated in final form. The controversies, however, have centered on the cost, and utility of FDA’s proposed requirements and not on the Agency’s legal authority to impose donor screening requirements in the first place or to strengthen those now on the books.²⁷⁸

The third component of FDA’s plan raises issues that are of more immediate interest, because they expose the limits of the Agency’s current statutory arsenal. In January 2001, just before President Clinton left office, FDA proposed a set of so-called “good tissue practice” regulations that would expand the duties of tissue banks and significantly enlarge the remedies available to the Agency.²⁷⁹ All of the new duties that FDA has proposed and all of the enforcement tools that it has claimed would rest, for their legal authority, on Section 361.²⁸⁰ None is based on the possibility that a bank’s tissues might be classed as drugs or devices, which might then permit FDA to rely on the FDCA.

It is not necessary here to resolve the legal objections that have been lodged against FDA’s proposal, but it is useful to describe the issues surrounding the limits of this ancient statute. The challenges to FDA’s proposal fall under three headings.

First, tissue banks question provisions of the proposed regulations that would prescribe how—and for what uses—tissue banks

²⁷⁵ See Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5,447, 5,449 (Jan. 19, 2001).

²⁷⁶ See 66 Fed. Reg. at 5,448-49.

²⁷⁷ See Suitability Determination for Donors of Human Cellular and Tissue-Based Products, 64 Fed. Reg. 52,696 (Sept. 30, 1999).

²⁷⁸ See 1994 AATB Letter, *supra* note 204, at 23-24.

²⁷⁹ Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement, 66 Fed. Reg. 1,508 (Jan. 8, 2001).

²⁸⁰ 66 Fed. Reg. at 1,509-10.

may label their products.²⁸¹ The announced aim of FDA’s proposed requirements is to limit “claims” for tissue use to those uses for whose utility there is convincing historical evidence.²⁸² Anticipating that this proposal might be challenged as exceeding the Agency’s disease prevention authority under Section 361, FDA made essentially the following argument: The failure of a tissue graft to perform as claimed could require corrective surgery and thus expose the recipient to the risk of disease—disease associated with surgery.²⁸³ Citing Section 361’s original purpose, tissue banks contend that it does not authorize requirements that are, at bottom, aimed at assuring clinical effectiveness.²⁸⁴

Several comments also question FDA’s legal authority to exercise the inspectional and enforcement powers that it has proposed.²⁸⁵ For example, FDA proposes to exercise inspectional powers over tissue banks that it could not exercise over manufacturers of most other products the FDCA gives it authority to regulate.²⁸⁶ Tissue banks point to the long history of congressional scrutiny of FDA’s inspectional powers under the FDCA, in which powers sought by the Agency have often been refused or granted only for limited purposes or narrowly defined products.²⁸⁷ If Congress, in the FDCA, the statute for which FDA is chiefly responsible, has withheld authority that the Agency now claims, they ask, is it plausible to construe a statute enacted before FDA was even created as conferring it?

²⁸¹ Letter from Richard J. Kagan, MD, President of American Association of Tissue Banks, to Dockets Management Branch, FDA 17 (May 8, 2001) (on file with author) [hereinafter 2001 AATB Letter]; 1994 AATB Letter, *supra* note 204, at 23-24.

²⁸² See Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement, 66 Fed. Reg. 1,508, 1,516-1,517 (Jan. 8, 2001).

²⁸³ Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement, 66 Fed. Reg. 1508-01, 1510 (Jan. 8, 2001) (to be codified at 21 C.F.R. pt. 1271).

²⁸⁴ 2001 AATB Letter, *supra* note 281. The legislative history demonstrates that “Section 361(a) authorizes regulations designed to prevent the transmission of communicable disease from a contaminated article to a human being. The FDA may not rely on Section 361(a) to promulgate regulations that have other objectives.” *Id.* at 18.

²⁸⁵ See *FDA Tissue Practices Rule is Criticized by Industry, Physicians*, FDA WEEK, June 1, 2001, at 14 [hereinafter *FDA Tissue Practices Rule is Criticized*]; 1994 AATB Letter, *supra* note 204, at 24-27 (describing the struggle by FDA to gain power to inspect manufacturing facilities).

²⁸⁶ See *FDA Tissue Practices Rule is Criticized*, *supra* note 285, at 14; 2001 AATB Letter, *supra* note 281, at 25.

²⁸⁷ See *FDA Tissue Practices Rule is Criticized*, *supra* note 285 at 14; 2001 AATB Letter, *supra* note 281, at 24-27.

Finally, comments challenge FDA's proposal to give its inspectors authority to order a tissue bank to cease operations if it is found out of compliance with the regulations governing screening, testing, processing, or storage.²⁸⁸ Under the proposal, such an order would have to set forth the Agency's grounds and describe procedures by which the order may be challenged administratively, but it could take effect in the meantime.²⁸⁹ In substance, an FDA inspector would be empowered to issue an administrative TRO, subject to challenge only after the fact. Tissue banks contend that this proposal would violate due process.²⁹⁰

3. Assessment

In 2002, roughly a decade after FDA became concerned about human tissue, two arguably contradictory propositions can be advanced. FDA's regulatory scheme seems well-entrenched and working reasonably well. The scheme rests on an enticingly open-ended statutory grant of authority, Section 361, which identifies a goal and accords wide discretion in fashioning requirements to meet the goal. However, FDA's capacity to mine this authority to support new requirements to meet what it judges to be the challenges of new technologies may be near its limits. The Agency has recognized that some tissue-based technologies raise issues of safety or effectiveness whose answers cannot be presumed, and it can be expected with increased frequency to turn instead to the more demanding, and costly, requirements of the FDCA for drugs and devices.

III. FDA ATTEMPTS TO REGULATE HUMAN CLONING

Readers will recall press reports in February 1997 that a team of researchers at the Roslin Institute in Scotland had successfully cloned a sheep which they named Dolly. The successful use of somatic cell nuclear transfer to produce a living mammal raised fears that humans could be cloned by similar means.²⁹¹ Within weeks

²⁸⁸ See *FDA Tissue Practices Rule is Criticized*, *supra* note 285, at 15; 2001 AATB Letter, *supra* note 281, at 30. This portion of the letter challenged the proposed 21 C.F.R. 1271.440. *Id.*

²⁸⁹ See Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement, 66 Fed. Reg. 1,508, 1,523-24 (Jan. 8, 2001).

²⁹⁰ See *FDA Tissue Practices Rule is Criticized*, *supra* note 285, at 15; 2001 AATB Letter, *supra* note 281, at 30-31.

²⁹¹ See generally, *To Clone or Not to Clone*, *CHRISTIAN CENTURY*, Mar. 19-26, 1997, at 286-88; Frank Bruni, *Experts Urge No Hasty Curbs on Cloning*, *N.Y. TIMES*, Mar. 14, 1997, at B2;

President Clinton banned federal funding of any attempt to clone human beings²⁹² and asked the National Bioethics Advisory Commission (NABC) to address the moral and ethical issues surrounding cloning.²⁹³ The Clinton administration also urged enactment of the "Cloning Prohibition Act of 1997," which would have banned the creation of human beings using somatic cell nuclear transfer. However, congressional interest in special cloning legislation soon slowed, partly as a result of lobbying by the scientific community and pharmaceutical industry, which feared that a statutory ban could stifle already widely-used or highly promising procedures.²⁹⁴

While Congress was deliberating, FDA suddenly announced that it already possessed authority to regulate cloning experiments. The Agency's position first came in the answer the acting FDA Commissioner gave to a question posed on a radio call-in-show.²⁹⁵ A few months later FDA repeated the claim that it had jurisdiction over any attempt to clone a human being—this time in a "Dear Colleague" letter to institutional review boards (IRBs) throughout the country.²⁹⁶ The letter explained that any such experiment was subject to the FDCA's investigational new drug requirements and could only be undertaken with FDA approval of an IND.

Kenneth L. Woodward, *Today the Sheep . . . Tomorrow the Shepherd?*, *Before Science Gets There, Ethicists Want Some Hard Questions Asked and Answered*, *NEWSWEEK*, Mar. 10, 1997, at 80; Robert Wright, *Can Souls Be Xeroxed?*, *TIME*, Mar. 10, 1997, at 73; *One Lamb, Much Fuss*, *THE LANCET*, Mar. 8, 1997, at 661; Nigel Williams, *Cloning Sparks Calls for New Laws*, *SCIENCE*, Mar. 7, 1997, at 1415; Declan Butler & Meredith Wadman, *Calls for Cloning Ban Sell Science Short*, *NATURE*, Mar. 6, 1997, at 8-9; Rick Weiss, *Lost in the Search for a Wolf Are Benefits in Sheep's Cloning*, *WASH. POST*, Mar. 3, 1997, at A3; Nancy J. Duff, *Clone with Caution: Don't Take Playing God Lightly*, *WASH. POST*, Mar. 2, 1997, at C1, C5; Jane Gross, *Thinking Twice About Cloning*, *N.Y. TIMES*, Feb. 27, 1997, at B3; George F. Will, *The Moral Hazards of Scientific Wonders*, *WASH. POST*, Feb. 25, 1997, at A17; *Cloning for Good or Evil*, *N.Y. TIMES*, Feb. 25, 1997, at A26; Robert Langreth, *Cloning Has Fascinating, Disturbing Potential*, *WALL ST. J.*, Feb. 24, 1997, at B1, B8.

²⁹² See Memorandum from William J. Clinton, The President, The White House, to the Heads of Executive Departments and Agencies (March 4, 1997).

²⁹³ See Clinton Urges Ban on Cloning of Humans, *CHRISTIAN CENTURY*, June 18, 1998.

²⁹⁴ See *Genetics: U. S. Doctors Urge Don't Pass Bad Cloning Law*, *GENE THERAPY WKLY*, Feb. 2, 1998; Diane Gianelli, *Cloning Ban May Hinder Research*, Oct. 20, 1997.

²⁹⁵ See Rick Weiss, *Human Cloning Will Be Regulated; FDA Asserts It Has Statutory Authority to Regulate Attempts at Human Cloning*, *WASH. POST*, Jan. 20, 1998, at A1.

²⁹⁶ See Stuart Nightingale, *Dear Colleague Letter* (Oct. 26, 1998), available at <http://www.fda.gov/oc/ohrt/irbletr.html>. [hereinafter Nightingale Letter] (last visited October 24, 2002) (asserting that "[FDA] has jurisdiction over clinical research using cloning technology to create a human being" under the Public Health Service Act and the Federal Food, Drug and Cosmetic Act and informing "IRBs of the regulatory process that is required before an investigator can proceed with such a clinical investigation").

Thus FDA thrust itself into a debate that has divided the public health community and still continues to embroil Congress. FDA's claim of existing authority merits close scrutiny precisely because Congress has failed to enact legislation setting limits on the use of this at once troubling and promising technology.²⁹⁷

A. FDA Claims Jurisdiction

No complete explanation of FDA's decision to assert jurisdiction over cloning has yet appeared. We therefore do not know whether, or to what extent, the Agency was pressured by the White House. The first signal that FDA would seek to regulate cloning was sent during a radio interview of Acting FDA Commissioner Dr. Michael Friedman. According to press accounts, Friedman reportedly declared: "Through the Food, Drug, and Cosmetic Act we do have the authority to regulate human cloning and we are prepared to assert that authority."²⁹⁸ He went on to say that FDA viewed human cloning as analogous to gene therapy, over which the Agency had years before asserted regulatory control.²⁹⁹

A few days later, FDA's position was reaffirmed in a letter from the Agency's Deputy Commissioner for External Affairs, Sharon Smith Holston, to Senator Edward Kennedy. Perhaps to support the Senator's view that pending legislation was not needed to achieve the immediate goal of prohibiting attempts to create human clones, Ms. Holston wrote:

FDA already has jurisdiction over such experiments. While FDA's authority does not address the larger question of whether or not creating a human being using cloning technology should be alto-

²⁹⁷ For a useful account of the efforts in Congress, see Elizabeth C. Price, *Does the FDA Have Authority to Regulate Human Cloning?*, 11 HARV. J.L. & TECH. 619, 625-26 (1998). See also Gregory J. Roskosz, *Human Cloning: Is the Reach of FDA Authority Too Far a Stretch?*, 30 SETON HALL L. REV. 464, 465 (2000); Valerie S. Rup, *Human Somatic Cell Nuclear Transfer Cloning, the Race to Regulate, and the Constitutionality of the Proposed Regulations*, 76 U. DET. MERCY L. REV. 1135, 1135-36 (1999).

²⁹⁸ Rick Weiss, *Human Cloning Will Be Regulated; FDA Asserts It Has Statutory Authority to Regulate Attempts At Human Cloning*, WASH. POST, Jan. 20, 1998, at A1; *FDA Has Authority to Regulate Cloning Technology As Biologic Product: Agency States after Chicago Physicist Seed Announces Plan for Human Cloning Clinic*, HEALTH NEWS DAILY, Jan. 13, 1998; *FDA Asserts Authority to Regulate Human Cloning: An Out for Industry Wary of Legislative Ban?*, THE PINK SHEET, Jan. 19, 1998.

²⁹⁹ For a history of FDA's role in overseeing gene therapy research, see Merrill & Javitt, *supra* note 4. There is a certain irony in Dr. Friedman's claim that human cloning is just another version of a medical technology that FDA was already regulating, given later reports of the failure of regulatory oversight by both the Agency and the National Institute of Health's Recombinant DNA Advisory Committee.

gether prohibited, this authority will ensure that such experimentation does not proceed until basic questions about safety are answered.³⁰⁰

Several months later on October 26, 1998, FDA's Associate Commissioner for Medical Affairs, Dr. Stuart Nightingale, sent the letter described above to the nation's several hundred institutional review boards. Dr. Nightingale's letter offered this explanation of FDA's position:

Clinical research using cloning technology to create a human being is subject to FDA regulation under the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act. Under these statutes and FDA's implementing regulations, before such research may begin, the sponsor of the research is required to submit to FDA an IND describing the proposed research plan; to obtain authorization from a properly constituted and functioning IRB; and to obtain a commitment from the investigators to obtain informed consent from all human subjects of the research. Such research may proceed only when an IND is in effect. Since FDA believes that there are major unresolved safety questions pertaining to the use of cloning technology to create a human being, until those questions are appropriately addressed in the IND, FDA would not permit any such investigation to proceed.

FDA may prohibit a sponsor from conducting a study proposed in an IND application (often referred to as placing the study on "clinical hold") for a variety of reasons. If the Agency finds that "human subjects are or would be exposed to an unreasonable and significant risk of illness or injury," that would be sufficient reason to put a study on clinical hold. . . .³⁰¹

Even read as a unit, these statements left crucial questions unanswered. None explained what applications of cloning technology FDA believed it has authority to regulate. Dr. Nightingale's letter employed Dr. Friedman's formulation—"clinical research using cloning technology to create a human being"—but did not indicate whether this concept encompassed only experiments whose immediate goal is the creation of a human being or extended as well to experiments whose results could advance understanding of how a human clone might be produced. Dr. Nightingale did clarify the means by which FDA would exert authority, i.e., through the process by which the Agency oversees clinical studies of new drugs. However, he did not offer IRBs much guidance on how they were to fulfill their responsibility to assess the "safety" of cloning experiments. Nor did he suggest whether IRBs should address other issues raised by proposed cloning research.

³⁰⁰ Letter from Sharon Smith Holston, Deputy Commissioner for External Affairs, Food and Drug Administration, to Senator Edward M. Kennedy (Feb. 10, 1998) (read by Senator Kennedy on the Senate floor and published at 144 CONG. REC. S561).

³⁰¹ Nightingale Letter, *supra* note 296.

FDA's invocation of its IND regime had the effect of imposing a theoretical legal moratorium on much domestic human cloning research.³⁰² The Agency's loose description of the kinds of experiments subject to its jurisdiction places investigators, and their sponsors, at legal risk if they fail to secure agency approval. There is no evidence that any researcher has since sought FDA (or IRB, for that matter) approval for any cloning experiment. This is not to suggest, though, that no such experiments have been undertaken surreptitiously.

Nearly two years after Dr. Nightingale's letter, FDA was induced to elaborate its legal rationale. No reports of actual attempts to clone a human had been reported, but a U.S. researcher and a colleague in Italy announced they were planning to produce the first human clone. In response, on March 28, 2001, the Oversight and Investigations Subcommittee of the House Committee on Energy and Commerce convened a hearing to inquire into the government's plans to regulate cloning research. The Director of FDA's CBER, Dr. Kathryn Zoon, was a featured witness.

In a prepared statement Dr. Zoon described the Agency's concerns and outlined the regulatory requirements that, she asserted, existing law imposed.

FDA views the use of cloning technology to clone a human being as a cause for public health concern. . . . Because of unresolved safety questions on the use of cloning technology to clone a human being, FDA would not permit the use of cloning technology to clone a human being at this time. . . . It is important to note that FDA's role in assessing the use of cloning technology to clone a human being is a scientific one. As recognized by the National Bioethics Advisory Commission, there are additional unresolved issues including the broader social and ethical implications of the use of cloning technology to clone a human being. Because of the profound moral, ethical, and scientific issues, the Administration is unequivocally opposed to the cloning of human beings.³⁰³

In her statement, Dr. Zoon seemed to send several related messages. The last quoted sentence sets forth the Bush administration position on cloning generally, and seems to draw a distinction between the "moral" and "ethical" concerns that animate the administration's opposition and FDA's "scientific" concerns about safety. Dr. Zoon did not suggest, however, that FDA is prepared to address

³⁰² Weiss, *supra* note 295, at A9.

³⁰³ *Issues Raised by Human Cloning Research: Hearing Before the House Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, 107th Cong. 79-81 (2001)* (statement of Kathryn C. Zoon, Director, Center for Biologics Evaluation and Research, Food and Drug Administration).

the "moral" or "ethical" issues, thus raising the implication that if the Agency's concerns about safety could be resolved, its regulatory responsibility will be fulfilled. She later acknowledged this implication when asked whether FDA would attempt to prevent an experiment if it were satisfied that the experiment posed no risk to the clone or its "mother" and she responded in the negative.³⁰⁴

Dr. Zoon went on to explain FDA's rationale:

FDA has the authority to regulate medical products, including biological products, drugs, and devices. The use of cloning technology to clone a human being would be subject to both the biologics provisions of the Public Health Service (PHS) Act and the drug and device provisions of the Federal Food, Drug, and Cosmetic (FD&C) Act. . . . Before such research could begin, the researcher must submit an IND request to FDA, which FDA would review to determine if such research could proceed. FDA believes that there are major unresolved safety questions on the use of cloning technology to clone a human being and therefore would not permit any such investigation to proceed at this time.³⁰⁵

Dr. Zoon's prepared statement and her responses to questions together represent the most extended description of FDA's concerns about human cloning and of the laws and regulations that, in the Agency's view, give it authority to regulate in this area. Even so, however, the Agency's formal account is surprisingly delphic. Repetition serves as a substitute for explanation. Perhaps most troubling is FDA's failure to explain how, or indeed whether, exploration of the ethical issues raised by cloning will be integrated with the Agency's efforts to address the more conventional, if not less difficult, questions about the safety of the procedure.

Given Congress' failure, so far, to enact legislation to restrict cloning research, it is conceivable that FDA's position will become or remain "law" by default. The legal bases of FDA's authority and, just as important, the Agency's capacity to address the serious issues raised by human cloning research, therefore deserve careful scrutiny. As a prelude to that review it is useful to describe FDA's role in regulating clinical research generally.

B. FDA's Oversight of Clinical Research

Federal oversight of medical research involving human subjects rests on two main foundations. The Department of Health and Human Services ("HHS"), FDA's parent, has jurisdiction over human research supported by HHS funds or conducted at institu-

³⁰⁴ *Id.* at 89-90.

³⁰⁵ *Id.* at 80-81.

tions that receive HHS funds.³⁰⁶ The other major body of clinical research subject to federal regulation is that sponsored by firms that need FDA approval to market new medical products.³⁰⁷ FDA oversight is, thus, a prominent feature of the medical research environment in this country. FDA's jurisdiction is not unlimited, however. The Agency's authority depends on the purpose for which research is undertaken and, just as importantly, on the substances or products administered to research subjects.

1. FDA's Legal Theory in Brief

The universe of articles over which FDA has regulatory authority consists chiefly of products marketed to improve human health³⁰⁸—drugs, medical devices, and biological products.³⁰⁹

³⁰⁶ HHS Fact Sheet: Protecting Research Subjects available at <http://www.hhs.gov/news/press/1999/pres/991222a.html> (last visited June 2, 2000).

³⁰⁷ Hutt & Merrill Text, *supra* note 8, at 21; Merrill, *Architecture of Government Regulation*, *supra* note 10, at 1753. Not all clinical studies of drugs and devices are sponsored by manufacturers or conducted for the purpose of gaining FDA approval for marketing. Many are sponsored by NIH, and thus are subject to federal oversight on that ground alone, and others are undertaken by individual investigators who obtain IND approval to study possible beneficial effects of agents approved for other indications, agents they cannot otherwise lawfully obtain. The majority of such studies, however, are manufacturer-sponsored and are undertaken to obtain evidence to support applications for marketing approval. *Id.*

³⁰⁸ FDA also regulates food and cosmetics and certain radiation-emitting products, like microwave ovens, development of these products rarely involves testing on human subjects. Our focus in this part is on FDA's authority to regulate products to which human beings are commonly exposed in experimental settings and its derivative authority to regulate such experiments. 21 U.S.C. § 321.

³⁰⁹ The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 343(r)(1)(B) and 343(r)(3) of this title or sections 343(r)(1)(B) and 343(r)(5)(D) of this title, is made in accordance with the requirements of section 343(r) of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 343(r)(6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement. FDCA, 21 U.S.C. § 321(g)(1)(1938).

The term "device" (except when used in paragraph (n) of this section and in sections 331(i), 343(f), 352(c), and 362(c) of this title) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is B (1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation,

FDA's authority over drugs and medical devices comes from the FDCA.³¹⁰ Its authority over biological products stems from section 351 of the laws now collectively codified as the PHSA.³¹¹ Practically all new human drugs must be approved by FDA before they may be marketed, as must new life-sustaining and implantable medical devices.³¹² Biological products, such as vaccines, similarly require FDA licensure.³¹³ It is FDA's power to regulate the market introduction of such products that is the source of its legal authority over clinical research.

To simplify, the following discussion focuses on the FDCA's requirements for "new drugs,"³¹⁴ for it is on these requirements that

treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purpose. FDCA, 21 U.S.C. § 321(h).

A biological product is defined as follows: "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man." PHSA, 42 U.S.C. § 262(i) (1944).

³¹⁰ FDCA, 21 U.S.C. §§ 301-397.

³¹¹ PHSA, 42 U.S.C. § 201.

³¹² Hutt & Merrill Text, *supra* note 8, at 752.

³¹³ *Id.* at 664.

³¹⁴ FDCA, 21 U.S.C. § 321 (p) (defining the term "new drug" as B (1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or (2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions). This complicated definition, made part of the FDCA in 1962, was intended to exclude from FDA's premarket approval requirements drugs marketed prior to the 1938 enactment of the Act for which physician or patient experience provided confirmation of safety and, later, effectiveness. While a few so-called "old" prescription medicines remain in use, e.g., digitalis, the vast majority of prescription drugs marketed in the U.S. have gone through FDA's new drug approval process, and any novel medical agent indisputably must satisfy the Agency's requirements.

This simplification does not undermine the fundamental accuracy of our description. Although the PHSA does not expressly authorize FDA to regulate premarketing research on biological products, the Agency has appropriately held that biologicals are also

FDA relies to support its jurisdiction over cloning experiments. Since 1962, the FDCA has required affirmative FDA approval for the marketing of any new drug and specified that, before granting approval, the Agency must have evidence that the drug is both safe and effective for the use(s) that the manufacturer intends to promote in labeling and advertising.³¹⁵ To obtain such evidence, the manufacturer must sponsor clinical trials in human subjects. Usually, the still-experimental drug must be shipped to the investigators who have agreed to conduct the clinical trials. To permit such shipment, Congress authorized FDA to grant exemptions for drugs shipped solely for investigational use.³¹⁶ The statute also directs FDA to impose conditions that the manufacturer must satisfy to qualify for exemption, i.e., to gain approval for clinical studies. These conditions are mainly designed to protect the safety and autonomy of study subjects.³¹⁷

Dr. Nightingale's letter to IRBs and Dr. Zoon's congressional testimony leave no doubt that, in asserting jurisdiction over cloning experiments, FDA is—or was—relying on its authority to regulate, i.e. to require approval for, clinical studies of unapproved new drugs.

2. *Alternative Theories*

Before evaluating this theory, we should examine other theories that the FDA presumably considered.³¹⁸

a. Section 361 of the PHSA

Readers will recall Section 361 of the PHSA, on which FDA has relied to erect its regulatory scheme for human tissue. In relevant

"drugs" and therefore subject, prior to marketing, to the FDCA's requirements for "investigational new drugs." Unlike drugs and biologicals, not all medical devices require premarket approval for safety and effectiveness, but a significant number—consisting of the highest-risk devices—do, and the FDCA authorizes FDA to oversee clinical research involving such devices. The oversight regime for "investigational devices" is similar to that for new drugs. See 21 C.F.R. § 5.701.

³¹⁵ Merrill, *Architecture of Government Regulation*, *supra* note 10, at 1800 (noting that FDA has required comprehensive premarket approval for therapeutic drugs since 1962).

³¹⁶ 21 U.S.C. § 355(i).

³¹⁷ 21 U.S.C. § 355.

³¹⁸ For an analysis of the alternative sources of FDA legal authority see Robert P. Brady & Molly S. Newberry, *FDA's Existing Statutory and Regulatory Authority Give the Agency the Broad Authority to Regulate the Cellular Materials Involved in Human Cloning*, FDA WK, Feb. 27, 1998, at 17.

part that section authorizes FDA "to make and enforce such regulations as in his 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. . . ."³¹⁹

Advocates for FDA regulation suggested that the Agency could rely on this language to regulate human cloning because of the risk of transmission of HIV and other infectious diseases from the donor(s) of cellular material to a clone or its "mother."³²⁰ While not facially implausible, this theory would have presented two difficulties that may explain FDA's failure to adopt it. First, while the measures authorized by Section 361 are broadly described, the end at which such measures must be aimed is not; the only goal that Congress has authorized the Agency to pursue is the prevention of communicable disease—a narrower target than the manifold concerns about cloning. Moreover, and more importantly, FDA could have invoked Section 361 only if it had been prepared to initiate rulemaking in accordance with the APA.³²¹ The section has no operative force in the absence of regulations. FDA *has* promulgated regulations governing human tissues based on Section 361³²² but they do not impose on tissue processors or on medical researchers any obligation to notify the Agency about, much less gain its approval for, research using tissue. The need for rulemaking to impose any *ex ante* restrictions on cloning experiments would have delayed regulation for months, perhaps longer, and undermined any administration claim of existing authority.

b. FDA's Human Tissue Scheme.

A second option pressed on FDA, according to unnamed officials who responded to reporters' inquiries, was to rely on the "FDA plan for cellular and tissue-based products,"³²³ the 1997 document we have already examined. FDA published final tissue regulations later that year.³²⁴ As recounted earlier, these regulations govern the recovery, processing, and distribution of transplantable human tis-

³¹⁹ 42 U.S.C. § 264.

³²⁰ Brady and Newberry, *supra* note 318, at 17.

³²¹ Administrative Procedure Act, 5 U.S.C. § 553.

³²² 21 C.F.R. § 1270 (1999).

³²³ Proposed Approach, *supra* note 260.

³²⁴ 62 Fed. Reg. 40,429 (1997) (codified at 21 C.F.R. Part 1270.1-43).

sue but they do not purport to impose any restrictions on the clinical use of appropriately screened and processed tissue. Accordingly, even if FDA had been prepared to argue that the cellular material used to produce a human clone fell within its definition of "human tissue,"³²⁵ this conclusion would not have enabled the Agency to require advance approval of any clinical experiments. To impose such a duty, while relying on Section 361, FDA would have had to amend its regulations.³²⁶

FDA's "plan for cellular and tissue-based products" does contemplate that some tissues will require clinical studies to demonstrate safety and effectiveness—a requirement that would be triggered by a determination that a tissue is a biological drug or Class III device.³²⁷ FDA's plan can therefore be read as predicting how the Agency might view human cloning but, standing alone, it cannot provide authority for the restrictions the Agency later sought to impose. FDA's tissue plan itself has never been promulgated as a regulation and it thus has no legal force.³²⁸ Moreover, it does not purport to require premarket approval—or impose restrictions on clinical experimentation—for any specific technology. The document discusses the criteria FDA will consider in deciding whether such requirements should apply to a technology but it leaves unclear the process by which such decisions will be made.³²⁹ Further-

³²⁵ 21 C.F.R. § 1270.3(j) (2002).

³²⁶ See PHS § 361 (42 U.S.C. § 264) (providing the FDA with authority to make and enforce regulations judged necessary "to prevent the introduction, transmission, or spread of communicable disease . . .").

³²⁷ Proposed Approach, *supra* note 260, at 12. FDA recognizes that a triage strategy of the kind it has outlined requires criteria for distinguishing between low-risk technologies and technologies that warrant more stringent oversight. To make such distinctions the plan says the Agency would focus on two questions: (1) Does the technology involve more than "minimal manipulation" of human material? (2) Is the material, however prepared, intended for an "homologous use," i.e., a use similar to the function it served in the donor? If the answer to the first question is "yes," or the answer to the second is "no," the technology is a candidate for regulation as a biological drug or, possibly, as a medical device. *Id.* at 13-15; see also discussion classifying tissue as a biological drug, *supra* notes 68-69 and accompanying text.

³²⁸ FDA did announce the availability of the plan by notice in the *Federal Register*, but the text of the document has never appeared there. 62 Fed. Reg. 9721-01 (codified at 21 C.F.R. Chapter I).

³²⁹ This is something of an overstatement. FDA has announced the establishment of an internal "Tissue Reference Group," consisting of officials from its Center for Biologics Evaluation and Research and its Center for Devices and Radiological Health, which is responsible for determining—so far as the Agency has authority to determine—how particular technologies should be regulated. 66 Fed. Reg. 42671-01 (August 14, 2001). Although the Agency has invited formal requests for determination from developers of technologies, the

more, the plan does not identify any source of authority to impose controls over research other than the premarket approval requirements of the FDCA and the Biologics Act.³³⁰

There is yet another reason why FDA might have found it awkward to invoke its plan for regulating cellular and tissue technologies as precedent for regulating cloning. The Agency's initial tissue regulations displayed a gap that makes its eagerness to regulate human cloning puzzling. Among the medical uses of human tissue, transplantation of donated sperm, eggs, or complete embryos to assist reproduction may be the most familiar. Yet, prior to 1999, FDA had taken no steps to regulate providers of reproductive tissues or to oversee the means by which reproductive tissues are recovered or the procedures in which they are used.³³¹ Indeed, when it promulgated its tissue regulations in 1997, the Agency expressly excluded reproductive tissue from their coverage.³³²

c. Cloning as Gene Therapy

When he claimed FDA jurisdiction over cloning, Acting FDA Commissioner Friedman likened the procedure to gene therapy.³³³ In her subsequent congressional testimony, CBER Director Zoon

process by which the TRG will arrive at and communicate its determinations remains ill-defined and ad hoc. No provision has been made for inviting, or allowing for, comments from third parties—physicians, patients, professional associations, or other developers of technology. See Proposed Approach, *supra* note 260, at 8-9 (discussing the classification of tissue as a biological drug).

³³⁰ The plan implies that before declaring that a particular cellular or tissue technology must meet more rigorous standards than the basic requirements for "conventional" tissues, FDA will announce its reasons and allow developers, users, and members of the public an opportunity to offer supporting or contradictory evidence and argument. See Proposed Approach, *supra* note 260.

³³¹ In 1998, the Agency indicated that at some time in the near future it would apply its general requirements for human tissue to entities engaged in the recovery and transplantation of reproductive tissue. See Proposed Rule: Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products, 63 Fed. Reg. 26,744 (May 14, 1998).

³³² See Human Tissue Intended for Transplantation, 62 Fed. Reg. 40429 (July 29, 1997). It is possible, perhaps even likely, that FDA was reluctant to acknowledge its authority to regulate a set of procedures that have excited intense interest, considerable controversy, and wide publicity. Proliferation of assisted reproduction services raises a set of questions almost as diverse and profound as those posed by human cloning. Furthermore, if the Agency were to enter the arena, it would surely face pressure from opponents of many of these services to go much further than "mere" public health concerns might lead it to go. Finally, in any settings FDA might confront real difficulty in establishing that the tissue in question had moved, or might move, in interstate commerce.

³³³ See *supra* notes 298-99 and accompanying text.

quoted from a 1993 *Federal Register* notice in which FDA announced that it considered somatic cell therapy products to be both biological products and drugs.³³⁴ The implication was that the statutory authority that supports FDA's regulation of gene therapy research also supports its jurisdiction over cloning.

FDA has long insisted that research protocols involving the insertion of somatic cells into human subjects must first have its approval.³³⁵ The Agency's explicit legal premise is that such experiments involve the administration of investigational drugs and are therefore subject to the controls authorized by the Section 505(i) of the FDCA.³³⁶ FDA's decade-old program is administered by CBER, which purports to review gene therapy protocols in the same way that it judges other experimental applications of biotechnology—but with an important variation.³³⁷ The novel element is a product of the original regime for federal oversight of recombinant DNA technology, which relied on the Recombinant DNA Advisory Committee (or RAC), an entity established by the National Institutes of Health in 1973.³³⁸ In recent years gene therapy protocols have been reviewed by both the RAC and CBER.³³⁹

FDA's regulation of gene therapy experiments may thus offer a precedent for asserting jurisdiction over cloning, but it does not provide an independent legal basis for the position announced by Dr. Friedman and later defended by Dr. Zoon. FDA's oversight of gene therapy research is not based on an explicit legislative grant of jurisdiction; rather, it is predicated on the premise—which I shall examine presently—that such experiments involve the administration of unapproved drugs, which makes them subject to the Agency's IND regulations. Furthermore, when it asserted authority over gene therapy experiments, FDA did something it has conspicuously failed to do with respect to human cloning research: The

³³⁴ See *supra* note 305 and accompanying text.

³³⁵ Merrill & Javitt, *supra* note 4.

³³⁶ 63 Fed. Reg. 26744. See *supra*, text accompanying notes 87-93 and accompanying text.

³³⁷ Merrill & Javitt, *supra* note 4.

³³⁸ *Id.* The RAC's original focus was on experiments that could result in the release of genetically altered organisms into the environment.

³³⁹ While at first the RAC and FDA were regulatory competitors, over time the two agencies have tended to specialize. See Merrill & Javitt, *supra* note 4. The RAC has concentrated on the ethical/societal issues posed by proposed experiments, while FDA has focused on familiar FDCA issues—the immediate risk to participants, the potential for therapeutic benefit, and the investigator's processes for preparing and administering the genetic material to be studied. See *id.*

Agency published an analysis of its authority and a description of its procedures in the *Federal Register* and invited public comment.³⁴⁰

3. Analysis of FDA Authority

We can now assess the plausibility of the legal theory on which FDA ultimately relied to assert jurisdiction over human cloning experiments. For any clinical experiment to be subject to FDA regulation, three conditions must be met. First, the procedure must involve the administration of an "article." Second, that article must fit the FDCA's definition of "drug" (or its definition of "device"). Finally, the article must be administered to a human subject.

The term "article" appears several times in the FDCA but it is not separately defined.³⁴¹ It is easy to think of drug dosage forms or medical instruments as "articles," but FDA has historically taken a more expansive view. For example, it considers a gene, alone or combined with an insertion vector such as a virus, to be a "drug." No court has confronted, much less affirmed this position, but most observers would now consider it well-established. Accordingly, FDA is on safe ground contending that the FDCA could apply to an experiment that involves the administration of genetic material to a human subject—assuming the other conditions are satisfied.

FDA should not have difficulty satisfying the third condition, i.e., that the article be administered to a human subject. It could be debated whether the cells injected with the genetic material of the human to be cloned and then transplanted into a surrogate's womb were administered to the "mother" or to the clone, but courts would likely conclude that this ambiguity is one for the Agency to resolve. If an experiment did not involve, or was not intended to produce, a human being, however, FDA would lack jurisdiction.³⁴²

³⁴⁰ Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, 58 Fed. Reg. 53,248 (Oct. 14, 1993).

³⁴¹ See 21 U.S.C. § 321.

³⁴² For the FDCA to apply, the article—or some component, such as a processing agent, preservative, or container—must also have been, or intended to be shipped in interstate commerce. One can imagine cloning experiments that might escape FDA regulation because they do not, directly or indirectly, have any interstate element, but most would not. Even so, the statement in the text could be misleading because FDA also exercises jurisdiction over the experimental use of new animal drugs under a separate provision of the FDCA. FDCA, 21 U.S.C. § 360(k); 21 U.S.C. § 360b; 21 C.F.R. § 511 (1999). Neither FDA nor anyone else, however, has suggested that this authority could support the Agency's jurisdiction over cloning research.

The second condition mentioned above requires more extended analysis, however. For FDA to have jurisdiction, an article must satisfy the FDCA's definition of "drug" or "device."³⁴³ For simplicity, I again focus on the Act's "drug" definition, which encompasses:

- (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- (C) articles (other than food) intended to affect the structure or function of the body of man or other animal³⁴⁴

Both clauses require an inquiry into the use for which an article is intended. The cases confirm that it is the seller's intention—ordinarily as demonstrated by labeling or advertising—that governs. However, we are considering procedures for which no labeling has been approved and no advertising has appeared. In the present context it would probably be the research plan itself that would be consulted to determine the use that the investigator intends.

From press accounts one can surmise what one prominent proponent of human cloning, Dr. Richard Seed, planned. Dr. Seed apparently intended to extract DNA from the cell of a human donor, inject that DNA into a separate cell (from another donor) from which the DNA had been removed, and then implant combined material into a woman for gestation. The resulting child would be a clone of the individual who donated the original DNA. Would this fall within FDA's jurisdiction?

There is little question that the procedure, if successful, would appeal to couples who are unable to procreate naturally.³⁴⁵ The procedure could also appeal to couples who risk transmitting hereditary diseases,³⁴⁶ but to suggest that it would therefore fall within the "disease" clause of the FDCA's drug definition could be a stretch. The procedure might be said to involve "prevention" if one objective were to produce a child free from the heritable condition of a potential "parent," but this would usually be an incidental effect,

³⁴³ As previously recounted, FDA also regulates, through premarket licensure, biological products under Section 351 of the PHS Act (42 U.S.C. § 264). The Agency has not interpreted Section 351 as authorizing it to oversee or restrict clinical research prior to licensure. Rather, to exert control over clinical trials of new biologics, FDA has declared them also to be "drugs" under the FDCA. See 38 Fed. Reg. 1404 (January 12, 1973); Weiss, *supra* note 295, at A1.

³⁴⁴ FDCA, 21 U.S.C. § 321(g)(1).

³⁴⁵ See L. Eisenberg, *The Outcome as Cause: Predestination and Human Cloning*, 1 J. MED. & PHIL. 318, 318-31 (1976).

³⁴⁶ See JOHN A. ROBERTSON, *CHILDREN OF CHOICE: FREEDOM AND THE NEW REPRODUCTIVE TECHNOLOGIES* (1994).

not a primary purpose, of the procedure. The "disease" clause of the drug definition does not seem a plausible source of FDA authority to regulate a procedure whose immediate goal is to clone a human being.³⁴⁷

Some "cloning experiments" could yield products over which FDA would clearly have jurisdiction. For example, there are suggestions that nuclear transfer could be used to grow human organs for transplantation or to create herds of genetically-engineered animals that could serve as "factories" for medicines. Experiments to evaluate such products in human subjects would be subject to FDA's IND jurisdiction, and their "manufacture" would be subject to agency oversight both at the clinical trial stage and, later, when approval for marketing was sought. But FDA jurisdiction would not attach until research yielded a product that was ready for administration to human subjects.

The second clause of the FDCA's drug definition is a more plausible source of FDA authority. The use of cloning technology—indeed any technology—to create a human being could be said to be "intended to affect the structure or function of the body of man . . ." ³⁴⁸ Congress almost surely contemplated an existing man (or woman) whose body an article could affect, but its words do not preclude a claim that the implantation of cells in a woman in order to clone a child would be intended to "affect" the body of the resulting clone. In any case, it would be hard to argue that the procedure was not intended to, or could not be expected to, affect the body of the mother.³⁴⁹

It is not necessary here to imagine which experimental applications of cloning technology FDA could legitimately regulate. What is clear is that FDCA's drug definition does not comfortably encompass all of the applications now awaiting investigation.³⁵⁰ Yet,

³⁴⁷ The possibility that the procedure might *cause* disease in the clone, though certainly of legitimate concern, would not be a basis for FDA jurisdiction. See PHS Act § 361, 42 U.S.C. § 264.

³⁴⁸ FDCA, 21 U.S.C. § 321(g)(1)(C).

³⁴⁹ FDA has long, and apparently without dispute, exercised jurisdiction over chemical agents intended to promote conception, presumably on the theory that they are intended to affect the function if not the structure of the would-be mother. This is not to say that it has asserted jurisdiction over all conception-promoting technologies. To date the Agency has conspicuously refrained from regulating sperm or ova or embryos donated to assist conception. John Henkel, *Safeguarding Human Tissue Transplants*, FDA CONSUMER, Sept. 1994, at 9.

³⁵⁰ The reader should not assume that the other statutory categories—"device" and "biological product"—would fill any gaps. FDA's authority to regulate clinical experiments in-

FDA's jurisdiction is not confined to products of which Congress was aware in 1938. The FDCA's definitions were drawn in broad terms so that the Agency could regulate later-discovered medical technologies and novel applications of old ones.³⁵¹ Given the breadth of the statutory language, FDA's interpretation might well be accorded deference in any judicial challenge to its assertion of jurisdiction over many, if not all, cloning experiments involving or designed to produce a human being.³⁵²

C. Has FDA Violated the Administrative Procedure Act?

There is another issue that needs to be explored, however, before concluding this analysis of FDA's legal authority. When an agency exercises lawmaking authority, the APA requires that it provide notice of its proposal and "give interested persons an opportunity to participate . . . through the submission of written data, views, or arguments."³⁵³ FDA has done neither of these. The APA also recognizes, however, that not all agency statements explaining their plans or their authority amount to administrative lawmaking. Interpretive rules and statements of agency policy are exempt from its notice and comment requirements.³⁵⁴

In asserting jurisdiction over human cloning experiments, FDA does not purport to be making new law. Yet there can be no question that FDA's successive statements were intended to alter the legal environment within which cloning research may proceed. FDA's statements arguably purport to explain legal requirements already in place, but their intended impact on researchers was as dramatic and emphatic as if Congress had enacted one of the anti-cloning bills before it.

FDA might argue that its utterances constituted statements of agency policy and thus were exempt from the APA's requirements. On this theory, FDA's statements, taken together, forecast the posi-

volving biological products depends on their fitting the FDCA drug definition. And the FDCA definition of "device" is in all relevant respects similar to the definition of drug. See *supra* note 309.

³⁵¹ *United States v. Article of Drug Bacto-Unidisk*, 394 U.S. 784, 798 (1969). *Brown & Williamson Tobacco Corp.*, 529 U.S. at 165 (Breyer, J., dissenting) (citing *Bacto-Unidisk*, 394 U.S. at 798).

³⁵² See *Chevron*, 467 U.S. at 844 (1984).

³⁵³ APA, 5 U.S.C. § 553(c).

³⁵⁴ APA, 5 U.S.C. § 553(b)(A). See generally, Robert Anthony, *Interpretive Rules, Policy Statements, Guidances, Manuals, and the Like—Should Federal Agencies Use Them to Bind the Public?*, 41 DUKE L. J. 1311 (1992).

tion that the Agency would adopt in some future rulemaking or, more plausibly, would advance in proceedings to enforce its IND regulations against researchers who undertook cloning experiments without approval. In response to a possible lack of notice claim, the Agency could say that it was under no obligation to issue any warning at all and could have proceeded on the premise that the statute and agency regulations—the IND regulations and perhaps gene therapy notices—spoke for themselves.³⁵⁵ One difficulty with this account is that FDA has never acknowledged that its position was contingent or subject to question.³⁵⁶ Rather, the Agency's message—as embodied in Dr. Nightingale's letter and Dr. Zoon's testimony—was that its jurisdiction is unequivocally conferred by statute and that the conditions for its exercise are already spelled out in the IND regulations.

Alternatively, FDA might argue that its statements constitute an "interpretive rule," and on this ground were exempt from the APA's rulemaking requirements. This explanation would also be problematic.³⁵⁷ FDA has generally published interpretive rules in the *Federal Register*. Here, FDA spurned such publication and has never attached the label "rule" to any of its pronouncements. Moreover, interpretive rules typically purport to explain, that is to interpret, language found in some indisputably binding statute or regulation. FDA's only extended discussions of cloning—Dr. Nightingale's letter and Dr. Zoon's testimony—do not refer to or squarely rely on language in the FDCA or the IND regulations.

Recent case law could undermine either rationale FDA might offer. Two relevant decisions involve FDA itself. In *Syncor Inter. Corp. v. Shalala*,³⁵⁸ the U.S. Court of Appeals for the D.C. Circuit considered a procedural challenge to a 1995 FDA publication entitled "Regulation of Positron Emission Tomography Radiopharmaceutical Drug Products; Guidance; Public Workshop." In this publication, which appeared in the "Notices" section of the Federal

³⁵⁵ Of course, FDA would have to acknowledge that in any enforcement action it would have the burden of showing that the researcher's material, and the purpose for which it was used, brought the experiment within the ambit of its IND regulations, properly interpreted. See *Gen. Elec. Co. v. EPA*, 53 F.3d 324 (D.C. Cir. 1995).

³⁵⁶ It is noteworthy that, in announcing its position, FDA did not allude to, much less rely upon the APA's exception for agency policy statements. See *supra* notes 296-300 and accompanying text.

³⁵⁷ Needless to say, FDA did not seek to take advantage of this exception either. See APA, 5 U.S.C. § 553(c).

³⁵⁸ *Syncor Inter. Corp. v. Shalala*, 127 F.3d 90, 92 (D.C. Cir. 1997).

Register, FDA announced that positron emission tomography radioactive pharmaceuticals ("PET drugs") were subject to regulation under the FDCA. The notice went on to list several sections of the Act that manufacturers of such drugs must satisfy.³⁵⁹ Syncor, a manufacturer of PET drugs, filed suit, contending that FDA's publication constituted a legislative rule that had not been adopted in accordance with the APA's procedures for rulemaking.³⁶⁰

In addressing this challenge, the D.C. Circuit refused the suggestion that FDA had engaged in an interpretive act. "[The 1995 publication] does not purport to construe any language in a relevant statute or regulation. Instead, FDA's rule uses wording consistent only with the invocation of its general rulemaking authority to extend its regulatory reach."³⁶¹ The court's analysis emphasizes that, as the term suggests, "interpretive rules" interpret existing laws or regulations. Moreover, the opinion suggests that when an agency wishes to extend its jurisdictional reach, it must comply with the APA.

In *Northwest Tissue Center v. Shalala*,³⁶² discussed in Part II, the Seventh Circuit confronted a challenge to FDA's attempt to regulate transplantable human heart valves as class III devices. Reviewing the procedure that FDA had followed in asserting jurisdiction,³⁶³ the court ruled that the processors had been deprived of an opportunity to comment on the Agency's determination that human heart valves were subject to regulation as medical devices. Neither of the Agency's earlier proceedings governing "replacement heart valves" had provided notice that the resulting rules might apply to allografts.³⁶⁴ In substance, the Seventh Circuit held that the processors were entitled to prior notice of, and an opportunity to comment

³⁵⁹ *Id.* at 92-93. These included section 505(i), 21 U.S.C. § 355(i), which prescribes conditions for the clinical study of unapproved drugs—the same requirements that FDA has said apply to cloning. 21 C.F.R. § 312.2(a) (1996).

³⁶⁰ *Id.* at 93; PHSA § 361 (42 U.S.C. § 264).

³⁶¹ *Id.* (citing *American Mining Congress v. Mine Safety & Health Admin.*, 995 F.2d 1106, 1112 (D.C. Cir. 1993)). In truth, the FDA notice could be said to represent a determination by FDA that PET drugs (all within the statutory category of "new drugs" subject to the requirements of section 505; in other words, an "interpretation" of that term. But the notice did not pause to explain this analysis. It merely asserted the Agency's bottom line.)

³⁶² 1 F.3d 522 (7th Cir. 1993).

³⁶³ *Id.* at 525-26.

³⁶⁴ *Id.* at 530.

on, FDA's determination that their products were to be regulated as Class III medical devices.³⁶⁵

These two cases suggest grounds on which FDA's assertion of jurisdiction over human cloning research could be challenged: The Agency's ex cathedra statements that cloning experiments are subject to the IND requirements amount to a "rule," subject to the APA's rulemaking requirements. The statements had the immediate effect of subjecting researchers to legal requirements they could not have anticipated, requirements whose violation may carry criminal as well as civil sanctions. They extended FDA jurisdiction into a new arena and imposed new obligations on parties never previously subject to its control.³⁶⁶

Other cases support this analysis. In *Appalachian Power Co. v. Environmental Protection Agency*,³⁶⁷ electric power companies challenged a "guidance" document, in which EPA explained to state agencies the requirements under the Clean Air Act, and implementing regulations, that must be met by state-administered permit systems for stationary industrial sources. Responding to EPA's claim that the document was not reviewable because it was not final or binding, the D.C. Circuit observed:

The phenomenon we see in this case is familiar. Congress passes a broadly worded statute. The Agency follows with regulations containing broad language, open-ended phrases, ambiguous standards, and the like. Then as years pass, the Agency issues circulars or guidance or memoranda, explaining, interpreting, defining and often expanding the commands in the regulations. . . . Law is made, without notice and comment, without public participation, and without publication in the Federal Register or the Code of Federal Regulations.

. . . If an agency acts as if a document issued at headquarters is controlling in the field, if it treats the document in the same manner

³⁶⁵ *See id.* at 536-537.

³⁶⁶ In truth, in both the PET drugs case and the allograft heart valves case, FDA could argue, and did, that its announcement represented a plausible interpretation of existing regulations. In the *Northwest Tissue* case, for example, the Agency claimed that heart valves recovered from cadavers fell within the category, "replacement heart valves," embraced by its regulations. Yet it was undeniably true that the Agency had not previously considered allograft valves—or the banks that processed them—subject to its authority. Accordingly, the banks were entitled to claim surprise when FDA abruptly announced that it was demanding compliance with requirements that the Agency had fashioned without consideration of their applicability to tissue and that were no longer open for public comment. Thus the flaw in FDA's reasoning was not its assertion that its statutory authority could extend to allograft valves, but its failure to provide advance notice and an opportunity for the processors to dispute that conclusion, or question the practical consequences that flowed from it.

³⁶⁷ *Appalachian Power Co. v. EPA*, 208 F.3d 1015 (D.C. Cir. 2000).

as it treats a legislative rule, if it bases enforcement actions on the policies or interpretations formulated in the document, if it leads private parties or state permitting agencies to believe that it will declare permits invalid unless they comply with the terms of the document, then the Agency's document is for all practical purposes "binding."³⁶⁸

*Sugar Cane Growers Cooperative of Florida v. Veneman*³⁶⁹ involved facts not unlike those presented by FDA's assertion of jurisdiction over cloning. There the U.S. Department of Agriculture announced, by press release, that it would renew the previous year's arrangements for providing subsidy payments to sugar growers. Florida cane sugar producers challenged the Department's announcement as a "rule" that had been promulgated without complying with the APA's requirements. USDA denied that its implementation plan constituted a rule of any kind, to which the court responded:

We have little difficulty . . . in rejecting this argument. The August 31 press release, the September Questions and Answers and most notably the September 7 Notice of Program Implementation set forth the bid submission procedures which all applicants must follow, the payment limitations of the program, and the sanctions that will be imposed on participants if they plant more in *future* years than in 2001. It is simply absurd to call this anything but a "rule by any other name."³⁷⁰

A ruling that FDA failed to comply with the APA's rulemaking requirements would vindicate the policy that the Agency itself long embraced.³⁷¹ In 1977, FDA incorporated in its administrative practice regulations a provision promising that it would invite comment before adopting *interpretive* regulations.³⁷² The Agency adhered to this commitment when it undertook to regulate clinical studies of genetic therapies in the early 1990s. On three occasions, as it elaborated its expectations for investigators and sponsors of gene therapy experiments, FDA described its plans in the Federal Register and invited comments from interested members of the pub-

³⁶⁸ *Id.* at 1020-21. Similarly, in *Tabb Lakes, Ltd. v. United States*, 715 F.Supp. 726 (E.D.Va. 1988), *aff'd without op.*, 885 F.2d 866 (4th Cir. 1989), the Fourth Circuit set aside, for failure to comply with APA procedures, a Corps of Engineers memorandum interpreting the scope of the Clean Water Act's definition of "navigable waters" in which dredge and fill operations required affirmative permission. The "interpretive" memorandum potentially extended the Corp's permit requirement to millions of new acres over which it had not previously exercised jurisdiction. See also Anthony, *supra* note 354, at 1373.

³⁶⁹ 289 F.3d 89 (D.C. Cir. 2002).

³⁷⁰ *Id.* at 96.

³⁷¹ See also, *Gen. Elec. Co. v. EPA*, 290 F.3d 377 (D.C. Cir. 2002); *Chamber of Commerce of the U.S. v. U.S. Dep't of Labor*, 174 F.3d 206 (D.C. Cir. 1999).

³⁷² 21 C.F.R. pt. 10 (1976).

lic.³⁷³ It is ironic that the Agency dispensed with any comparable formalities when claiming authority to regulate human cloning—a technology Acting Commissioner Freedman likened to gene therapy.³⁷⁴

More than a technical legal issue is at stake here. FDA may believe that all it has done is explain that "experiments to clone a human being" are a form of gene therapy and are therefore subject to the standards the Agency has long applied to such treatments. The reality is different. FDA's unilateral declarations have not just stifled objections from sponsors and researchers; they diverted public discussion of the serious questions surrounding the role, conduct, and oversight of cloning research. None of the Agency's statements say whether its requirements apply only to experiments whose immediate aim is to produce a human clone or extend to any research whose results might facilitate the eventual cloning of a human being. They do not detail the safety concerns that ostensibly inspired the Agency to act, nor do they offer guidance to IRBs on how to assess those concerns. Even more significantly, while the statements acknowledge that there are broader issues surrounding cloning, they offer no hint of how these issues might be addressed in a regulatory process that historically has been concerned primarily with clinical design and patient safety.

D. The Possible Appeal of FDA Regulation

Despite uncertainty about its legal authority and serious reservations about its procedures, some may believe that FDA is well-suited to oversee human cloning research. FDA administers a regulatory regime whose outlines are familiar to medical researchers and whose requirements can be made operational immediately. The Agency's assertion of jurisdiction ostensibly provided interim control of a provocative technology until more finely calibrated requirements could be developed. FDA regulation may also offer flexibility. While the general requirements that researchers must follow are spelled out in regulations and supporting guidelines, lo-

³⁷³ Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, 58 Fed. Reg. 53,248 (Oct. 14, 1993); Draft of "Points to Consider in Human Somatic Cell and Gene Therapy," 56 Fed. Reg. 61,022 (Nov. 29, 1991); Recombinant DNA Research; Request for Comment on "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols," 54 Fed. Reg. 10,956 (Mar. 15, 1989); see also Merrill & Javitt, *supra* note 4.

³⁷⁴ See *supra* note 299 and accompanying text (discussing similarities between cloning and gene therapy technologies).

cal IRBs, and indeed FDA itself, presumably could consider research proposals on an individual basis.

Furthermore, there are many who would defend FDA oversight as preferable to the likely alternative, a legislative ban on all human cloning research. It is worth recalling that one response to Dolly's birth was a flood of legislative proposals at both the federal and state levels to ban cloning.³⁷⁵ More than half the state legislatures considered some form of anti-cloning legislation.³⁷⁶ While opponents of cloning sought an outright ban on all experiments, professional and industry organizations feared that legislation would end promising genetic research.³⁷⁷ For them, the discovery of latent FDA jurisdiction emerged as a flexible alternative to quite possibly futile efforts to craft finely-tuned controls through the charged legislative process.

The technical challenges that still confront legislators are compounded by the nature of the cloning debate. The controversy over cloning is closely linked to other hotly contested issues of reproductive freedom.³⁷⁸ In these circumstances, the more flexible regime offered by FDA held special appeal for both the research community and the pharmaceutical industry.

One can understand the concerns of both groups but their competing fears—of a legislative ban or of no ban at all—may have obscured a flaw in the solution offered by FDA. For the Agency's intervention not only displaced debate over the content of regulatory controls; it stifled discussion of FDA's own capacity to assess the issues that kindled that debate in the first place.

The argument for FDA jurisdiction is strongest when one focuses on the medical concerns raised by the possibility of human cloning. FDA's regulatory regime is structured to ensure the safety of new medical technologies before they are deployed in the clinic. FDA, and the IRBs on which it relies to help oversee clinical re-

³⁷⁵ See Diane M. Gianelli, *Congress Weighs Ban on Cloning*, AM. MED. NEWS (Feb. 23, 1998).

³⁷⁶ See NATIONAL BIOETHICS ADVISORY COMM'N, *Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Comm'n* 104, tbl.1 (1997) [hereinafter *Cloning Human Beings*] (detailing anti-cloning legislation proposed at both the federal and state level).

³⁷⁷ Helen Dewar, *Human Cloning Ban Sidetracked; Senate Vote Deals Amendment Second Setback in a Week*, N.Y. TIMES, June 19, 2002, at A4.

³⁷⁸ See Gianelli, *supra* note 294. See Henry T. Greely, *Banning Human Cloning: A Study in the Difficulties of Defining Science*, 8 CAL. INTERDISCIPLINARY L.J. 136 (1998). The California legislation recounted above managers to cover all proven forms of cloning technology, but did not reach viable, although untested, cloning techniques.

search, routinely address the safety of dramatic scientific advances and novel medical applications. By insisting that researchers demonstrate that experiments are not likely to harm subjects, FDA could help ensure that research involuntary humans does not proceed until there is a high degree of confidence in the technology.³⁷⁹

It is not possible to describe all of the hazards that cloning a human being might present, but several have been identified. The technology is unreliable and involves high error rates.³⁸⁰ The risk of fetal and neonatal death, not to mention the dangers to the mothers pregnant with clones, would counsel against any attempt to clone a human being until the success rate is greatly increased.³⁸¹ In addition, the technical complexity of the cell manipulation processes used in cloning raises the possibility that even were a live child produced, he or she could suffer from severe birth or developmental defects.³⁸²

The role FDA has claimed should oblige it to assess not only the risks—physical, psychological, and moral—of human cloning, but also the potential benefits as well. Professor George Annas was prompted to declare; “the good news is I think finally we have a technology that we can all agree shouldn't be used,”³⁸³ such claims do not go unchallenged. Supporters of continued research call attention as well to the potential benefits that cloning technology offers.³⁸⁴

One benefit that cloning offers is its potential to enable childless couples to produce children incorporating their own genetic material.³⁸⁵ To the extent that cloning may offer advantages over

³⁷⁹ See *Cloning Human Beings*, *supra* note 376 (stating “There is virtually universal concern regarding the current safety of attempting to use [cloning] in human beings.”).

³⁸⁰ See I. Wilmut et al., *Viable Offspring Derived from Fetal and Adult Mammalian Cells*, 385 NATURE 811 (1997).

³⁸¹ See Rick Weiss, *Cloning Shows Serious Health Risks*, WASH. POST, May 10, 1999 at A1.

³⁸² See Rick Weiss, *Cloning Suddenly has the Government's Attention*, INT. HERALD TRIB., March 7, 1997 (noting the concern of Harold Varmus, director of the National Institute of Health, that an old cell used to clone could have developed genetic mutations over the years leading to a predisposition to certain diseases like cancer in cloned individuals).

³⁸³ Virginia I. Postrel, *Fatalist Attraction: the Dubious Case Against Fooling Mother Nature; Biotechnological Advances*, REASON, July 1997, at 4.

³⁸⁴ See *Banning Federal Funds for Human Cloning Research: Hearing Before the House Subcommittee on Technology, of the Committee on Science*, 105th Congress at 1997 WL 465224 (statement of Alison Taunton-Rigby, Ph.D., President, Aquila Pharmaceuticals, and spokesperson for the Biotechnology Industry Organization).

³⁸⁵ See *Ethics and Theology: A Continuation of the National Discussion on Human Cloning, Before the Senate Subcommittee on Public Health and Safety, of the Committee on Labor and Human*

other reproductive technologies, this may provide a powerful justification for continued human cloning research. Another potential use of cloning technology is the possibility of producing harvestable organs for transplant.³⁸⁶ It is conceivable that the technology could be used to grow organs genetically identical to those that have failed. Cloning might also be used, in conjunction with gene targeting, to produce animals whose organs could be transplanted into humans.³⁸⁷ In addition, the combination of gene targeting and cloning should enable scientists to study the effect of specific genes, and the process of cell differentiation, more closely.³⁸⁸

The specific technique used to produce Dolly could also be a potential source of benefits.³⁸⁹ The Roslin scientists have suggested that somatic nuclear cell transfer could be of great benefit to agriculture, allowing the production of such beneficial new strains as cattle with leaner meat and cows that produce low-fat milk.³⁹⁰ Many firms see the new technology as a means to produce livestock which can produce in their own milk, pharmacological products for treating human diseases or organs for transplantation.³⁹¹

However, the potential benefits by themselves do not justify the use of this technology; important moral and ethical questions must also be addressed. Any system for evaluating human cloning experiments must be equipped to weigh ethical concerns as well as the scientific possibilities. And the truth is that FDA has not shown that it is equipped to address or resolve these questions. The clinicians, scientists, and administrators who work at FDA, able though they may be, do not have any claim to experience in making the kind of judgments that the prospect of human cloning demands.

FDA bases its jurisdiction on the FDCA provision that requires the Agency authority to approve any shipment (and thus almost

Resources, 105th Congress at 1997 WL 329510 (Statement by John A. Robertson, University of Texas Law School).

³⁸⁶ Robert Sanchez, *Professor Leads Seminar on Ethics of Cloning*, CHI. DAILY HERALD, April 10, 2002, at 3.

³⁸⁷ See Rick Weiss, *In Organ Quest, Cloning Pigs May Be the Easy Part*, WASH. POST, Mar. 20, 2000, at A7.

³⁸⁸ *Banning Federal Funds for Human Cloning Research: Hearing Before the House Subcommittee on Technology, of the Committee on Science*, 105th Cong. at 1997 WL 465224 (statement of Alison Taunton-Rigby, Ph.D., President, Aquila Pharmaceuticals, and Spokesperson for the Biotechnology Industry Organization).

³⁸⁹ See Justin Gillis, *Cloned Cows Are Fetching Big Bucks*, WASH. POST, Mar. 25, 2001, at A1.

³⁹⁰ Graeme Leech, *The Great Cattle Clone Drive*, THE AUSTRALIAN, July 6, 1998, at Features 10.

³⁹¹ See Richard A. Merrill & Bryan J. Rose, *FDA Regulation of Human Cloning: Usurpation or Statesmanship?*, 15 HARV. J.L. & TECH. 85, 92 (2001).

any administration) of an "investigational drug."³⁹² Section 505(i) directs FDA to establish conditions for granting such approval. It specifies that FDA shall require the submission of preclinical studies, the investigator's assurance of supervision, and the maintenance of records and submission of reports to enable FDA to evaluate the drug's safety and effectiveness.³⁹³ The statute also directs FDA to require investigators to inform research subjects that the drug is being administered for investigational purposes and to secure their consent to participate.³⁹⁴

FDA may impose other conditions "necessary for the protection of the public health."³⁹⁵ Among the most important of these is the requirement that any study be approved by a qualified IRB.³⁹⁶ I would not argue that no words in the several pages that comprise FDA's regulations could be construed as authorizing agency reviewers, or a responsible IRB, to explore the ethical questions presented by a proposed cloning study. But the regulatory text does not suggest that such an inquiry is contemplated.

To be sure, FDA has not suggested that it is eager to mediate the contending ethical and moral arguments over cloning. Dr. Zoon's testimony suggests that the Agency views its role as limited to evaluating the safety of proposed experiments.³⁹⁷ The consequences of this conservative posture are not reassuring, however. It seems likely that, when confronted with a proposed study, FDA officials would find it impossible to ignore the broader issues.

If FDA were determined to limit its review to the immediate safety of the study participants, the Agency would face pressure to arrange for a second forum in which the broader issues raised by cloning experiments could be debated. No such forum has been legally chartered. The RAC has statutory authority to review and approve (or reject) proposed studies that have the requisite link to

³⁹² 21 U.S.C. § 355(i) (2002).

³⁹³ 21 U.S.C. § 355(i).

³⁹⁴ 21 U.S.C. § 355(i).

³⁹⁵ 21 U.S.C. § 355(i).

³⁹⁶ 21 C.F.R. pt. 56.

³⁹⁷ See *Issues Raised by Human Cloning Research: Hearing Before the House Subcommittee on Oversight and Investigations, Committee on Energy and Commerce*, 107th Cong. 79-81 (2001) (statement of Kathryn C. Zoon, Director, Center for Biologics Evaluation and Research, Food and Drug Administration); Letter From Sharon Smith Holston, Deputy Commissioner for External Affairs, Food and Drug Administration, to Senator Edward M. Kennedy (Feb. 10, 1998) (read by Senator Kennedy on the Senate floor and published at 144 CONG. REC. S561).

federal funding, but its jurisdiction does not extend to studies sponsored by the private sector.

The importance of the moral and ethical issues surrounding cloning underscores another limitation of FDA's traditional oversight of clinical research. FDA review of proposed clinical studies occurs largely outside public view in order to protect the confidentiality of sponsors' proprietary material.³⁹⁸ Most new therapies are sponsored by for-profit firms that are aiming at commercial markets, and any oversight process must assure protection for their proprietary rights.³⁹⁹ This same reasoning would apply to proposed cloning experiments sponsored by commercial firms. But assuring confidentiality would hamper, and quite possibly preclude, the public debate.

E. Is FDA up to the Challenge?

I am not the first to question FDA's qualifications to regulate cloning research. In November 1998, a few weeks after distribution of Dr. Nightingale's letter to IRBs, the press reported a speech by Dr. David Kessler, who had recently become Dean of Medicine at Yale University after a widely publicized tour as FDA Commissioner. According to the report, Dr. Kessler expressed no doubts about FDA's legal authority to regulate cloning research, but argued that the Agency lacks the regulatory framework and the resources to prevent the cloning of a human being or other potentially unethical or unsafe biomedical experiments.

There is a difference between saying you have jurisdiction and knowing how to do it thoughtfully There is no question that under the law FDA can regulate cloning. The question is, does the agency know how to regulate and does it have the resources to do so.⁴⁰⁰

IV. CONCLUSION

The FDA's responses to novel technologies examined in these two case studies display both the strengths and weaknesses of the agency and its statutory armentarium. In each case FDA sought to address risks to public health that might otherwise have gone unregulated. Each initiative required imagination but also entailed risks: the risk of legal defeat, the risk of failure, the risk of appearing

³⁹⁸ Merrill & Rose, *supra* note 391, at 139.

³⁹⁹ *Id.*

⁴⁰⁰ Steve Usdin, *Kessler's Doubts*, *BIOCENTURY*, November 16, 1998, at A1.

inept. In neither instance has FDA entirely avoided missteps but in the case of cloning, however, the agency's errors were in my view fundamental.

A. The Common Themes

Certain themes characterize FDA's regulation of human tissue and its vestigial effort to address the challenge of human cloning. As in other contexts, the agency has relied—indeed has had to rely—on laws enacted in a different era, long before either technology was imagined. FDA's assertion of jurisdiction over cloning tests the very limits of its statutory authority, but this alone is not unprecedented nor necessarily illegitimate. FDA has assumed oversight of other novel medical technologies and the common feature—use in the delivery of medical care—may lead to an assumption the Congress expects the agency to assume responsibility.

There is one inconvenient consequence of FDA's readiness to regulate new technologies under FDCA. The Act's definitions of "drug" and "device" are capacious, but its requirements for technologies that fall within these categories are not as plastic. Reliance on the FDCA as the source of agency jurisdiction brings a good deal of baggage, the most significant being the need to secure agency approval for both clinical experimentation and ultimate commercialization. These requirements can be burdensome and expensive to satisfy, and they are applied in an institutional setting that is not accessible to skeptics, critics, or even supporters of technology.

Another disconcerting feature of my two studies—a narrow sample to be sure—is FDA's propensity for procedural missteps. When it declared allograft heart valves to be medical devices immediately subject to requirements adopted years earlier for a different set of products, the agency not only took a legal risk; it abridged basic rights of parties potentially subject to regulation, as the Seventh Circuit ultimately ruled. FDA arguably violated the Administrative Procedure Act again in December 1993, when it promulgated its "interim" tissue regulations without prior opportunity for comment. The agency's unilateral action was never directly challenged in court, but the district judge in the *Biodynamics* litigation made clear his doubts that FDA had "good cause" to invoke the APA's exception from rulemaking.

I have made clear my view that FDA probably violated the APA when it announced, on public radio, that cloning experiments were subject to its jurisdiction and required its approval to proceed.

This is, to be sure, a contestable conclusion. One could draft a Federal Register document that purported, expressly, to "interpret" the FDCA's drug definition as encompassing the genetic material that would be implanted in a surrogate mother's womb to produce a clone. But FDA did not do this, nor did it ever invite members of the public, including the research community, to address either its authority to regulate under existing law or the substance of the requirements it was prepared to enforce. It pursued a course that evaded public debate about its authority, its procedures, and its capacity to address the questions at the center of this country's debate over this at once promising and threatening technology.

B. FDA's Tissue Program

After some missteps, FDA's effort to assert control over human tissue has evolved into a balanced program for addressing the central public health problem that initially precipitated the agency's involvement. This is not to say that FDA's requirements are all finely calibrated or consistently enforced; individual banks doubtless could provide stories of overreaching by agency inspectors, who in turn could describe conditions or practices that fall far short of acceptable standards. In general, however, FDA has so far struck a reasonable balance between public health protection, on the one hand, and the constraints of its own budget and tissue bank resources, on the other.

While credit for this success is shared, two features of the current scheme are particularly noteworthy. First, once the "shock" of unannounced, immediate, unilateral regulation receded, the tissue program's evolution has been the product of a public dialogue among the agency, public health authorities, and tissue providers. This dialogue has occurred within the familiar framework bounded by Federal Register proposals, submission of comments, and agency preambles that address, and sometimes even confirm changes in response to, criticisms from a diverse and thinly capitalized industry. It has continued in meetings hosted by FDA and at conferences sponsored by professional associations that speak for many tissue banks and transplant surgeons. Second, FDA has successfully enlisted the cooperation of the American Association of Tissue Banks and professed its reliance on AATB's standards and accreditation

new drugs or class III devices—can be a cumbersome instrument for achieving agency goals. Of course, the serendipitous availability of Section 361 of the PHSA was critical. Not only did its language appear to fit the need of the moment, but its generous authorization of regulatory measures—to achieve a limited end—made it possible for FDA to tailor its regulatory requirements to meet the immediate challenge.

FDA's tissue program is not entirely an open book. The procedures of the agency's Tissue Reference Group remain mysterious, and the standards that tribunal applies in judging whether a tissue-based product may be treated as "mere" tissue or requires more comprehensive regulation as a biological drug or medical device remain controversial. Furthermore, FDA is clearly pressing the outer limits of its authority under Section 361. The language and history of that provision suggest that the agency goes too far when it argues that it may regulate tissue performance because graft failure may expose recipients who must undergo corrective surgery to the risk of disease from that source. FDA's "good tissue practice" proposal also strains credulity when it contemplates enforcement measures that Congress has never been persuaded to add to the FDCA and that, accordingly, FDA could not employ against makers of ordinary drugs or devices. So far the agency has not addressed the serious questions raised about the scope of its authority under Section 361.

C. FDA's Moratorium on Cloning

FDA's pronouncements—from Dr. Freidman, Dr. Nightingale, and later CBER Director Dr. Zoon—that it has jurisdiction over cloning experiments, which require agency approval, raise questions about both the agency's authority and its procedures. I have already stated my belief that the agency violated the APA in proceeding as it did. It is my suspicion that FDA's at once abrupt initiative was inspired by the White House, which may have become concerned that Congress would ban attempts to clone human embryos for any purpose. It is not plausible that Dr. Friedman would have answered the radio host's question as he did without advance clearance by HHS Secretary Donna Shalala and, at least indirectly, the White House.

Is it not surprising that FDA has never acknowledged this

Zoon's testimony in June 2001. And even then FDA made no effort to elicit support for, or address questions about, its assertion of jurisdiction.

A more serious criticism of FDA's actions is warranted. By invoking requirements that it applies to clinical trials involving investigational drugs, FDA sought to channel research proposals into a regulatory system that is ill-designed to ventilate the issues at the center of the debate about cloning. The safety of any procedure to produce a human clone is important, of course, but the deeper questions are whether such procedures ought to be attempted and whether the promise of "therapeutic cloning" justifies separate treatment in a regime that would forbid cloning for the specific purpose of creating a human being. These are not the kind of questions FDA routinely confronts. They are questions beyond the ken, and certainly the authority, of IRBs. Moreover, the framework within which questions about the design, purpose, and progress of conventional clinical trials are addressed does not permit, much less encourage, participation by the wide range of interests that variously support or oppose cloning.

Perhaps most troubling is the purpose for which FDA's regulatory authority was invoked. The IND provisions of the FDCA and FDA's implementing regulations are designed to assure that clinical studies of potential therapies proceed in circumstances where the welfare of participants is protected, where their autonomy is respected, and where the investigation is designed to yield scientifically meaningful information. These requirements may not be designed to facilitate clinical research, but they clearly are not meant to stifle it altogether. FDA asserted jurisdiction over cloning experiments so that such experiments would not proceed at all.

COMMENTS AND NOTES