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## The History of FDA Regulation of Biotechnology in the Twentieth Century

### Abstract

This paper attempts to provide a chronological history of the significant events and influences that have shaped the regulation of biotechnology by the Federal Food and Drug Administration. This paper first chronicles the evolution of each of the separate fields of regulation into which biological products are categorized by the FDA (drugs, biologics, devices, and foods). Part III of this paper then discusses the first call for governmental regulation of biotechnology and the struggle for regulatory form that this shift in administrative authority created. Part IV describes the Coordinated Framework for the Regulation of Biotechnology. Part V discusses subsequent efforts, both Congressional and administrative, to reform the regulation of biotechnology by FDA.

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## I. Introduction

Twenty-five years ago, Harvard researchers isolated and cloned the first complete mammalian gene, which encoded a component of hemoglobin in rabbits. Today, researchers and regulators are trying to cope with the implications of the newfound ability to clone complete mammals, including humans. The rapid pace of discovery in the biotechnological sciences has created substantial difficulties for the Federal Food and Drug Administration (FDA), which ensures the safety and efficacy of many of the products of biological research.<sup>1</sup>The speed of

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<sup>1</sup>The Office of Technology Assessment defines biotechnology as “any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop micro-organisms for specific uses... Biotechnology is the most recent phase in a historical continuum of the use of biological organisms for practical purposes.” Office of Technology Assessment, *Commercial Biotechnology: An International Analysis* at 3 (Jan. 1984); U.S. General Accounting Office, *Biotechnology: Agriculture’s Regulatory System Needs Clarification* at 8 (Mar. 1986) (Report to the Chairman, House Committee on Science and Technology). A brief chronology of landmark events in biotechnology includes:

- 1944 Avery, MacLeod, and McCarty demonstrate that deoxyribonucleic acid (DNA) is the genetic material utilized by most living organisms.
- 1953 Watson and Crick discover the double-helical structure of DNA.
- 1969 Isolation of a complete gene by a Harvard research team.
- 1973 Boyer and Cohen functionally insert a toad gene into a bacterium, which marks the beginning of genetic engineering.
- 1977 A human gene is cloned.
- 1980 Insertion of a human gene (coding for interferon) into a bacterium.
- 1980 Cline *et al.* create a transgenic animal, a genetically-modified mouse
- 1982 FDA approves a genetically-engineered drug, recombinant insulin produced in bacteria.
- 1983 Scientists at Cetus Corp. develop a technique for rapid and consistent *in vitro* replication of DNA, called the polymerase chain reaction (PCR).
- 1986 FDA approves a genetically-engineered vaccine for use in humans, used to inoculate against Hepatitis B.
- 1988 The United States Patent and Trademark Office awards to Harvard University a patent for a genetically-modified animal.
- 1990 Launch of a project to sequence every gene in humans, named the Human Genome Project.
- 1990 Gene therapy developed for use in humans, first performed by W. French Anderson on a four-year-old girl to treat an immune disorder called ADA deficiency.
- 1990 FDA approves a recombinant product called Chymosin for use in food.
- 1992 NIH files patent applications on thousands of gene fragments.
- 1992 The U.S. Army begins collecting blood and tissue samples from all new recruits as part of a genetic dog tag program aimed at better identification of soldiers killed in combat.
- 1992 *In vitro* testing of human embryos for genetic abnormalities.
- 1993 Cloning of human embryos, kept alive for several days in a laboratory

biotechnological logical discovery necessarily requires rapid product approval by regulators, as any substantial regulatory delay in the introduction of new biological products could result in those products becoming obsolete before they ever reach the consumer market. Additionally, the rapid spread of many modern diseases, such as AIDS, has exerted enormous pressure upon FDA to expedite approval or pre-approve possible therapeutic products, as delay in approving a potential cure may harm more people than any potential adverse effects of that product.

Acting contrary to these pressures to speed approval, however, is the reluctance of FDA to approve novel products with little clinical testing data. Because knowledge of effect far too often exceeds knowledge of cause in biotechnology, a thorough evaluation of the safety and efficacy of biological products requires extensive experimentation and analysis, particularly when considering long-term adverse effects.

These conflicting requirements for the regulation of biological products have produced a system of administrative oversight that is especially fluid and dynamic.

FDA has traditionally insisted that only an initial product-by-product review

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1993 Production of a rough map of all human chromosomes.

1994 FDA approves a recombinant food, a genetically-modified tomato.

1995 J. Craig Ventner and TIGR announce the sequencing of the first complete genome, that of the bacterium *Haemophilus influenzae*.

1997 Cloning of a complete animal, a sheep named Dolly.

1998 Cloning of eight identical calves utilizing cells from a single adult cow.

For a more extensive listing of noteworthy events in the development of biotechnology, see Michael J. Malinowski & Maureen A. O'Rourke, *A False Start? The Impact of Federal Policy on the Genotechnology Industry*, 13 YALE J. ON REG. 163 (Winter 1996); Michael D. Lemonick & Dick Thompson, *From Mendel to Monica*, TIME, January 11, 1999; Michael D. Lemonick & Dick Thompson, *Racing to Map Our DNA*, TIME, January 11, 1999.

of applications would allow FDA sufficient ability to adapt quickly to changes in the biotechnology field, in order to impose sufficient regulatory protections to ensure product safety while retaining FDA's ability to expedite or accelerate the approval process both for new products that pose little risk of injury or for classes of products that either have proven safe and effective or are desperately needed by terminally-ill patients.

As a result of the level of innovation and compromise present in the FDA product approval process, the status of legislation governing FDA approval of products derived from biotechnology is often far behind the actual administrative regulations and practices utilized by FDA examiners. This trend is especially evident in the recent set of Congressional reforms to FDA procedures and practices contained within the FDA Modernization Act of 1997, many of which were already available informally to product manufacturers through FDA administrative efforts and initiatives to speed the approval process and thereby access by the public to novel therapies.

Thus, applicants that have an understanding of current FDA procedures in combination with an ability to predict areas in which FDA is likely to compromise possess a substantial competitive advantage. This ability to predict changes in FDA approval policy derives in part from a knowledge of the standard ways in which FDA policy has evolved historically, the pressures and influences that prompted those historical changes, and an appreciation of the influences that exist currently and their likely effect; however, no concise treatment of the historical development of these policies, pressures, and influences exists. The

purpose of this article, therefore, is to attempt to identify and analyze the major historical changes and influences that have shaped the regulation of biotechnology by FDA during the twentieth century.

## II.

### FDA Regulatory Authority Prior to the Biotechnology Era (1902 - 1976)

Throughout the duration of its regulation of biotechnology, FDA has steadfastly maintained that “the agency need not establish new administrative procedures to deal with generic concerns about biotechnology.”<sup>2</sup>As a result of this policy, products of biotechnology do not comprise a distinct product group within FDA, but are instead categorized on a product-by-product basis as a “food”, “drug”, “device”, or “biologic”—four standard product areas of FDA jurisdiction (excluding cosmetics).<sup>3</sup> This dependence upon pre-existing product areas causes FDA approval of products of biotechnology to be strongly influenced by shifts in FDA’s general treatment of each of the four product areas, thus, a thorough understanding of each of the four categories and their evolution is necessary for a complete understanding of the process of FDA regulation of

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<sup>2</sup>Statement of Policy for Regulating Biotechnology Products, Food and Drug Administration, 51 Fed.Reg. 23,309 (1986). See also Curtis A. Kin, *Coming Soon to the “Genetic Supermarket” Near You*, 48 STAN. L. REV. 1573 (July 1996); Peter Barton Hutt & Richard A. Merrill, *Food and Drug Law*, Second Edition, Foundation Press, Inc., Westbury, New York, 1991.

<sup>3</sup>See 1991 FDA Guidelines, 56 Fed.Reg. 58,756 (1991). See also Tanya E. Karwaki, *The FDA and the Biotechnology Industry: A Symbiotic Relationship?*, 71 WASH. L. REV. 821 (July 1996).

biotechnology.

### A. Regulation of Drugs

PURE FOOD AND DRUGS ACT OF 1906 Congress first granted FDA significant authority to regulate drugs under the Pure Food and Drugs Act of 1906 (the “1906 Act”).<sup>4</sup> The 1906 Act prohibited interstate

commerce in “adulterated” or “misbranded” drugs.<sup>5</sup> The 1906 Act provided for both civil and criminal penalties for violation of its provisions.<sup>6</sup> A product used in interstate commerce will constitute a “drug” under the 1906 Act if it was either “recognized in the United States Pharmacopoeia or National Formulary for internal or external use. . . [or] intended to be used for the cure, mitigation, or prevention of either man or other animals.”<sup>7</sup> Thus, the determination of whether a product constitutes a “drug” under the 1906 Act turned in large part upon the use of the product intended by the manufacturer.<sup>8</sup> A drug was considered to be “adulterated” under the 1906 Act if “it differs from the standard of strength, quality, or purity” set forth in the Pharmacopoeia or Formulary, “if its strength or purity fall below the professed standard or quality under which it is sold”.<sup>9</sup> A drug was considered to be “misbranded” if “it be an imitation of or offered for

<sup>4</sup>34 Stat. 768 (June 30, 1906) (repealed in 1938).

<sup>5</sup>Pure Food and Drugs Act § 1, 34 Stat. at 768.

<sup>6</sup>*Id.*

<sup>7</sup>Pure Food and Drugs Act § 6, 34 Stat. at 769, codified as amended at 21 U.S.C. § 321(g)(1)(B).

<sup>8</sup>This currently, in determining such “intended” use, FDA is “not bound by the manufacturer’s subjective claims of intent but can find actual therapeutic intent on the basis of objective evidence. *National Nutritional Foods Association v. Mathews*, 557 F.2d 325, 334 (2d Cir. 1977).

<sup>9</sup>Pure Food and Drugs Act § 7, 34 Stat. at 769-70, codified as amended at 21 U.S.C. § 351(a)(1).

sale under the name of another article. . . [or] if the contents. . . as originally put up shall have been removed. . . and other contents shall have been placed in the package, or if the package fail to bear a statement on the label of the quantity or proportion of [certain enumerated substances].<sup>10</sup> Adulteration and misbranding are considered separate violations and may be prosecuted separately or jointly.<sup>11</sup> Criminal violations of the 1906 Act required a showing of intent or past violations of the Act.<sup>12</sup> The 1906 Act granted FDA limited administrative authority to ensure compliance with the requirements and prohibitions of the Act, authorizing FDA to collect samples of drugs for analysis and seize any adulterated or misbranded drugs.<sup>13</sup>

SHERLEY In 1911, the Supreme Court substantially limited the scope of the 1906 Act by AMENDMENT OF 1912 interpreting the definition of “misbranded” to prohibit only claims that were false or

misleading as they related to the identity or ingredients of the drug mixture, but not to prohibit false or misleading claims regarding the therapeutic effects of a drug.<sup>14</sup> Congress remedied this limitation of the 1906 Act by enacting the Sherley Amendment of 1912, which changed the definition of “misbranded”

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<sup>10</sup>Pure Food and Drugs Act ♣ 8, 34 Stat. at 770, codified as amended at 21 U.S.C. ♣ 351(a), (j). The enumerated substances that were required to be disclosed in the labeling were “alcohol, morphine, opium, cocaine, heroin, alpha or beta eucaine, chloroform, cannabis indica, chloral hydrate, or acetanilide, or any derivative or preparation of any such substances”. *Id.*

<sup>11</sup>See e.g. *United States v. Jamieson-McKames Pharms.*, 651 F.2d 532, 535 (8th Cir. 1981).

<sup>12</sup>21 U.S.C. ♣ 333. See also Erica L. Niezgoda & Maureen M. Richardson, *Federal Food and Drug Act Violations*, 35 AM. CRIM. L.REV. 767 (Spring 1998).

<sup>13</sup>Pure Food and Drugs Act ♣♣ 10, 11, 34 Stat. at 771-2, codified as amended at 21 U.S.C. ♣ 360.

<sup>14</sup>*U.S. v. Johnson*, 221 U.S. 488 (1911).



under the 1906 Act to include a “package or label [that] shall bear or contain any statement... regarding the curative or therapeutic effect of such article or any of the ingredients or substances contained therein, which is false and fraudulent.”<sup>15</sup> Although this formulation fully addressed the concerns of the Supreme Court that the 1906 Act did not grant authority to punish false statements of opinion, the new definition of “misbranded” proved slightly problematic, as it possessed the additional requirement that the seller actually be aware that the claims were false (“false *and* fraudulent”).

Although the 1906 Act, as amended by the Sherley Amendment, sketched the initial framework for the regulation of drugs by FDA, with the development of modern drugs, it soon proved inadequate to ensure public safety. In 1937, over seventy people were poisoned to death as a result of ingestion of a drug known as “Elixir Sulfanilamide”.<sup>16</sup> The manufacturer of this “Elixir” dissolved the drug sulfanilamide, a powder, in the solvent diethylene glycol in order to produce a liquid preparation of the drug. Once the fatal product was identified, it became clear that simple tests in animals, or even a review of published medical literature, would have revealed the poisonous nature of the Elixir combination; however, after the resultant deaths, the only basis of authority under the 1906 Act for FDA intervention to remove the Elixir from the public market was that the preparation was not actually an “elixir” (a title which only strictly applies to

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<sup>15</sup>37 Stat. 416, Ch. 352 (Aug. 23, 1912). See Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1735 (November 1996)

<sup>16</sup>Hutt & Merrill, *supra*, note 2, at 476.

products utilizing an alcohol-based solvent) and that the product was therefore misbranded.

FEDERAL           As a result of this incident, Congress realized that FDA  
could not effectively  
FOOD, DRUG,  
AND           safeguard the public against injury from adulterated products  
through the 1906 Act  
COSMETIC

ACT OF 1938   system of post-marketing review and testing, and, shortly thereafter, Congress repealed the 1906 Act and enacted the Federal Food, Drug, and Cosmetic Act of 1938 (the “1938 Act”), in order to provide FDA with authority for premarketing review of drugs.<sup>17</sup> The 1938 Act expanded the definition of drug to include “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals”.<sup>18</sup> The 1938 Act prohibited the introduction into interstate commerce of any “new drug”, which it defined as any “drug” that was not “generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof”.<sup>19</sup> Under the 1938 Act, a manufacturer could only bring a “new drug” to market if the drug was the subject of a new drug application (NDA) filed with FDA that FDA allowed to become effective.<sup>20</sup> In order to allow manufacturers to conduct clini-

<sup>17</sup>52 Stat. 1040, Ch. 675, codified as amended at 21 U.S.C. § 301 *et seq.* (June 25, 1938).

<sup>18</sup>Federal Food, Drug, and Cosmetics Act §201(g), 52 Stat. at 1041.

<sup>19</sup>Federal Food, Drug, and Cosmetics Act § 201(p)(1), 52 Stat. at 1,040-1. *See also* Merrill, *supra*, note 16.

<sup>20</sup>Federal Food, Drug, and Cosmetics Act § 505(a), 52 Stat. at 1,052.

cal trials on humans to collect sufficient data to support an NDA application, the 1938 Act authorized FDA to grant exemptions from this general prohibition for “investigational drugs” that are the subject of an investigational new drug application (IND) filed with FDA.<sup>21</sup> Additionally, the 1938 Act allowed FDA to seek injunction against manufacturers instead of merely seizing offending products.<sup>22</sup> The 1938 Act expanded the definition of “adulterated” drugs, as well as redefining the term “misleading” to mean that the labeling was “misleading” because it “fails to reveal facts material in the light of . . . representations [made in the labeling] or material with respect to consequences which may result from the use of the article to which the labeling relates”.<sup>23</sup> This new definition of “misleading” reflected changes in the state of medical evidence and in the views of courts toward FDA’s exercise of misbranding jurisdiction. This new definition also solved the problems created by the Sherley Amendment by no longer requiring FDA to present evidence concerning the intent or state of mind of the manufacturer; FDA needed only demonstrate that the product did not meet the claims of its labeling.

The 1938 Act, like the 1906 Act, provided for both criminal and civil penal-

<sup>21</sup>Drug Amendments ♣ 103(b), 76 Stat. at 783, codified at 21 U.S.C. ♣ 355(i).

<sup>22</sup>Federal Food, Drug, and Cosmetics Act ♣ 302, 52 Stat. at 1,043.

<sup>23</sup>Federal Food, Drug, and Cosmetics Act ♣ 201(n), 52 Stat. at 1041 (misleading). The 1938 Act defined “adulterated” as a drug that “(1) consists in whole or in part of any filthy, putrid, or decomposed substance; or (2) if it has been prepared, packaged, or held under insanitary conditions whereby it may have been rendered injurious to health; or (3) if . . . its container is composed . . . of any poisonous or deleterious substance which may render the contents injurious to health; or . . . [4] if its strength differs from, or its quality or purity falls below, the standard set forth in [an official compendium]”. Federal Food, Drug, and Cosmetics Act ♣ 501(a), 52 Stat. at 1049.

ties for violations of its provisions.<sup>24</sup> In addition, courts added a strict liability gloss to the 1938 prohibitions: a corporate officer could be convicted for criminal violations of the 1938 Act without intent or past violations if the authority possessed by that corporate officer placed them in “responsible relation” to “the furtherance of the transaction which the statute outlaws”.<sup>25</sup>

The 1938 Act also increased the administrative authority of FDA to enforce compliance with the requirements of the Act. The 1938 Act authorized FDA to conduct inspections of drug manufacturing facilities.<sup>26</sup> Although FDA inspections were subject to reasonable time and manner limitations, the scope of such an inspection can be very broad.<sup>27</sup> FDA inspectors are not required to state a reason for conducting an inspection or to state any expected findings.<sup>28</sup> FDA inspectors may inspect all manufacturing areas of the facility, including containers and vehicles, may take batch samples, and may seize any offending products.<sup>29</sup> While the 1938 Act significantly increased the ability of FDA to safeguard the public, the Act possessed several significant problems. Under the Act, a manufacturer could introduce a product into the market if the manufacturer itself believed that the product was “generally recognized as safe”, leaving

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<sup>24</sup>21 U.S.C. § 333.

<sup>25</sup>*United States v. Dotterweich*, 320 U.S. at 285 (1943). See Niezgoda and Richardson, note 12, *supra*.

<sup>26</sup>Federal Food, Drug, and Cosmetics Act § 704, 52 Stat. at 1057.

<sup>27</sup>*Id.*, also as codified at 21 U.S.C. § 374(a); Niezgoda and Richardson, *supra*, note 8.

<sup>28</sup>*Id.*

<sup>29</sup>*Id.*, also as codified at 21 U.S.C. §§ 374(a), (c), and (d).

FDA to contest the manufacturer's assessment. Even if manufacturers conceded that a product was a "new drug" and thereby required the filing of an NDA, FDA did not possess the authority to force the manufacturer to delay marketing the product while FDA evaluated the NDA (beyond a 180 day statutory waiting period), but merely possessed authority to declare an NDA ineffective after its evaluation. This second problem was compounded by the overwhelming volume of NDAs submitted to FDA under the 1938 Act.<sup>30</sup> When evaluating an NDA, FDA was formally limited under the 1938 Act to considering only the safety of the product, and not its therapeutic effectiveness. Once an NDA became effective for a given product, other manufacturers began production of similar versions of the product under the assumption that such generic, or "me-too", drugs were also considered "generally recognized as safe" and thereby covered under the pioneer NDA.

While the authority granted to FDA under the 1938 Act was in actuality limited to assessment of only the safety of a "new drug", FDA reviewers often considered the therapeutic efficacy of the drugs as well.<sup>31</sup> FDA took the position that the concept of drug safety can be viewed as a risk-benefit calculus, and, therefore, some consideration of efficacy—the benefit in the calculus—is inherent in the determination of safety. As a result, the concept of FDA statutory review of efficacy was foreshadowed long in advance by administrative necessities.

The value of this informal FDA review of drug efficacy was highlighted by birth defects caused by a new sedative introduced in Europe in 1957. This sedative,

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<sup>30</sup>Within five years after the passage of the 1938 Act, over 4,000 NDAs had been submitted to FDA. Hutt & Merrill, *supra*, note 2, at 477.

<sup>31</sup>See Merrill, *supra*, note 16.

Thalidomide, was widely prescribed to patients in Europe, including pregnant women. The administration of Thalidomide to pregnant women resulted in a variety of related children's birth defects known as phocomelia (in which the most common defect was missing or highly-malformed limbs).<sup>32</sup> Thalidomide was the subject of therapeutic trials before the FDA when its harmful effects were discovered, and, consequently, was never released for use in the United States.

DRUG                    In the aftermath of the Thalidomide controversy, Congress enacted the Drug AMENDMENTS OF 1962    Amendments of 1962 (the "1962 Amendments") in order to dramatically expand the

authority of FDA.<sup>33</sup> This new regulatory system enacted in the 1962 Amendments provided FDA with the authority to create the "modern" system of drug regulation. The 1962 Amendments forbid the shipment in interstate commerce of any new drug that was not the subject of an NDA approved by—and not merely filed with—FDA, thereby transforming the role of FDA from policeman to gatekeeper.<sup>34</sup> The breadth of this prohibition, acting alone, prevented manufacturers from conducting research on humans to demonstrate the safety and efficacy of any new drug without the prior approval of FDA, because the shipment of such new-but-unapproved drugs for use in humans would violate the 1962 Amendments. As under the 1938 Act, in order to allow manufacturers

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<sup>32</sup>See Merrill, *supra*, note 16.

<sup>33</sup>Pub. L. No. 87-781, 76 Stat. 780, codified as amended in various sections of 21 U.S.C. (Oct. 10, 1962).

<sup>34</sup>Drug Amendments ♣104, 76 Stat. at 784, codified at 21 U.S.C. ♣ 355(a).

to conduct clinical trials on humans, the 1962 Amendments authorized FDA to grant exemptions from this general prohibition for “investigational drugs” that are the subject of an investigational new drug application (IND) filed with FDA.<sup>35</sup>

The 1962 Amendments explicitly directed FDA to confirm the effectiveness of each new drug in addition to its overall safety, which dramatically increased the scope of FDA approval power.<sup>36</sup>The 1962 Act required that a manufacturer demonstrate the effectiveness of a new drug by “substantial evidence. . . consisting of adequate and well-controlled investigations, including clinical investigations”.<sup>37</sup> Because safety is evaluated on a product basis, an approved product is arguably safe for all uses; by contrast, efficacy is evaluated on the basis of therapeutic purpose, thus FDA decided that each different therapeutic use of a product requires individual approval under the 1962 Amendments. This meant that all new therapeutic uses of a product required the pre-approval of FDA by submission of a Supplemental New Drug Application (SNDA) by the drug manufacturer.

The 1962 Amendments, by directing FDA to assess efficacy, also allowed FDA to acquire effective control over the design and implementation of the clinical trials process. Because the 1962 Amendments required FDA approval of a new drug prior to marketing, manufacturers were forced to follow FDA directives in

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<sup>35</sup>Drug Amendments ♣ 103(b), 76 Stat. at 783, codified at 21 U.S.C. ♣ 355(i).

<sup>36</sup>Drug Amendments ♣ 102, 76 Stat. at 781, codified at 21 U.S.C. ♣ 321.

<sup>37</sup>21 U.S.C. ♣ 355(d).

clinical experiment design and conduct, or risk disapproval by FDA. This NDA approval power allowed FDA to dictate the design and scope of pre-clinical research as well.

The modern clinical trial process as defined by FDA under the 1962 Amendments possesses five discrete stages. The initial (or “preclinical”) phase consists of laboratory research conducted in animals to demonstrate threshold safety and therapeutic efficacy in order to support an IND application. IND applications must contain an identification of the active and inactive components of the product, manufacturing data, proposed labeling, identification and experience of the principal investigators, a limited environmental impact analysis, putative therapeutic uses, preferred route of administration, a summary of all pharmacological and toxicological data and testing, and a proposal for a clinical research protocol.<sup>38</sup> Once an IND is filed with FDA, manufacturers can commence the first set of experiments in humans.

Experiments in humans conducted under an effective IND are referred to as “clinical trials”. FDA has traditionally required that clinical trials take the form of three separate research protocols, or “phases”, although FDA by administrative compromise often allows wide latitude in the design of the overall experiments. The purpose of the first set of research protocols, commonly referred to as “Phase I” clinical trials, is to determine a “safe” dosage range, assess toxi-

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<sup>38</sup>21 C.F.R. ♣♣ 312.23, 355. See also Michael J. Malinowski & Maureen A. O’Rourke, *A False Start? The Impact of Federal Policy on the Genotechnology Industry*, 13 YALE J. ON REG. 163, 208 (Winter 1996); Sandra H. Cuttler, *The Food and Drug Administration’s Regulation of Genetically Engineered Human Drugs*, 1 J. PHARMACY & L. 191, 198 (1992/1993).



cology, and test various routes of administration of the compound, and Phase I trials are normally conducted using completely healthy patients.<sup>39</sup>Phase I clinical trials generally last less than one year and include less than one-hundred patients.<sup>40</sup>Over two-thirds of drugs that enter Phase I clinical trials do not prove safe or practical.<sup>41</sup>New drugs that demonstrate preliminary safety in healthy patients during Phase I trials are then tested in clinical trials involving patients that possess the target disease that the drugs are intended to treat. This second set of trials, called “Phase II” clinical trials, generally lasts less than two years and involves 100 to 300 patients.<sup>42</sup>The purpose of Phase II clinical trials is to determine an “effective” dosage range and to further assess toxicology and administration in patients actually possessing the target disease. One-third of drugs entering Phase II clinical trials do not prove effective or practical.<sup>43</sup>Drugs that demonstrate preliminary safety and efficacy in Phases I and II, respectively, then undergo a final thorough set of clinical testing to in order to fully assess the risks and benefits of the drug, to discover any adverse effects resulting from long-term administration, and to obtain all data necessary for complete and accurate labeling of the ultimate product by physicians.<sup>44</sup>This final set of clini-

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<sup>39</sup>See Teresa Pechulis Buono, *Biotechnology-Derived Pharmaceuticals: Harmonizing Regional Regulations*, 18 SUFFOLK TRANSNAT'L L. REV. 133 (Winter 1995); Malinowski and O'Rourke, *supra*, note 27, at 208.

<sup>40</sup>Michael A. Friedman, M.D., Lead Deputy Commissioner, Food and Drug Administration, *Statement Before the Committee on Government Reform and Oversight, United States House of Representatives*, April 22, 1998 (available on-line at [www.fda.gov](http://www.fda.gov)).

<sup>41</sup>Malinowski and O'Rourke, *supra*, note 27, at 209; *see also* Friedman, *supra*, note 29.

<sup>42</sup>Malinowski and O'Rourke, *supra*, note 27, at 209.

<sup>43</sup>*Id.*

<sup>44</sup>*Id.*

cal trials, called “Phase III” clinical trials, often lasts over three years and can involve up to several thousand patients.<sup>45</sup> Normally, researchers work closely with FDA when designing and conducting Phase III trials in order to ensure that the research produces sufficient data to adequately support the ultimate application to FDA for approval to market the drug.

Upon completion of Phase III clinical trials, the data regarding the safety and efficacy of the drug is submitted to FDA in the form of an NDA. The 1938 Act requires an NDA to contain a “full report” of the clinical trials research, which FDA has interpreted to include a complete report of all clinical and pre-clinical research, including the records of every patient involved in the research, a list of all active and inactive components of the product to be marketed, a statement of the composition of the active (drug) ingredient of the product, a complete description of the methods of manufacture, processing, and packaging of the product, copies of the proposed labeling for the product, and samples of the product if requested by FDA.<sup>46</sup>In addition to requiring FDA to assess the efficacy of all new drugs, the 1962 Amendment also required FDA, after a two-year waiting period, to apply the efficacy standard to all drugs marketed prior to 1962. This requirement immediately posed two major difficulties for FDA. First, review panels appointed by FDA to assess the efficacy of drugs covered by NDAs approved prior to 1962 found several thousand such drugs to be “ineffective”, however, the 1962 Amendments granted the manufacturers of such drugs the

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<sup>45</sup>Friedman, *supra*, note 40.

<sup>46</sup>21 U.S.C. §355(b)(1)(A); *see also* Merrill, *supra*, note 16, at 1784; Cuttler, *supra*, note 27, at 199.

right to an administrative hearing prior to FDA disapproval of their previously-approved NDAs.<sup>47</sup> FDA quickly realized that conducting several thousand such administrative trials would be a practical impossibility. To circumvent these administrative hearings, FDA issued administrative guidelines to redefine both the adequate design of clinical trials and the acceptable level of clinical data required to support an NDA and to require that all NDAs be supported by efficacy data matching the then-current clinical norms among academic researchers.<sup>48</sup> This redefinition had little, if any, effect upon pending clinical trials and NDA applications then before FDA, however, the redefinition all but ensured that any pre-1962 drug challenged by FDA would have inadequate clinical evidence supporting efficacy to allow a lengthy administrative defense of the pre-1962 NDA. The Supreme Court ultimately upheld FDA's reinterpetive tactic.<sup>49</sup> The second major difficulty in applying the efficacy standard to pre-1962 drugs involved generic products marketed without FDA approval. Prior to 1962, once a pioneer NDA became effective for a given drug, other manufacturers often began production of similar versions of the product under the assumption that all such generic drugs were also covered under the pioneer NDA, and thereby were "generally recognized as safe". Tens of thousands of generic products had been marketed in this fashion prior to 1962.<sup>50</sup> Because these generic drugs were never

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<sup>47</sup>Merrill, *supra*, note 16, at 1,770.

<sup>48</sup>35 Fed.Reg. 7,250 (1970); *see also* Merrill, *supra*, note 16, at 1,770. Note that the 1938 Act required an NDA to be supported by "substantial evidence...[including] adequate and well-controlled...clinical investigations". 21 U.S.C. ♣♣ 355(d)-(e).

<sup>49</sup>*Weinberger v. Hynson, Westcott, and Dunning*, 412 U.S. 609 (1973)

<sup>50</sup>Merrill, *supra*, note 16, at 1,770.

the subject of individual NDAs, FDA disallowance of a previously-approved pioneer NDA, as described above, would have no effect upon generics, as they never actually possessed any administrative approval to be disapproved.<sup>51</sup> Once a pioneer NDA was disallowed, FDA could challenge each individual manufacturer in court to enjoin the sale of the generic product, however, FDA would bear the burden of proof in each case and would have to challenge each product individually. Again, FDA realized the practical impossibility involved in conducting such administrative challenges. To resolve this problem, FDA took the position that all generic drugs are administratively dependent upon the effectiveness of the applicable pioneer NDA, thus disapproval of the pioneer NDA would immediately result in disapproval of the related generics. The Supreme Court ultimately upheld this position as well.<sup>52</sup> Further utilizing its increased administrative authority granted under the 1962 Amendments, FDA expanded its authority over drug manufacturers in two important areas. First, FDA asserted that all material modifications to any aspect of an approved product required prior approval from FDA, as any such change could effect the efficacy of a product and thereby potentially invalidate the approval of its NDA.<sup>53</sup> Thus, changes in labeling, methods of manufacture, and packaging must be reported in addition to changes in the ingredients of the products. Manufacturers were required to submit any such product changes as an Supplemental New Drug

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<sup>51</sup>*Id.*

<sup>52</sup>*USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655 (1973). *See also* Merrill, *supra*, note 16, at 1,770.

<sup>53</sup>Merrill, *supra*, note 16, at 1,775.

Application (SNDA) to FDA, a procedure which almost treated the product changes as if they constituted a new therapeutic use for the product.

Second, FDA asserted that an approved product would be considered “adulterated”, and thereby subject to disallowance and seizure, if the method of manufacture of the product did not conform to a set of objective standards promulgated by FDA, regardless of the actual safety and efficacy of the product. First published in 1963, these regulations, referred to as “current good manufacturing practices” (CGMPs), have been continually amended by FDA to reflect changes in technology and to contain specialized requirements for individual categories of products.<sup>54</sup> To further ensure compliance with CGMPs, FDA has asserted that no SNDA will be approved unless the manufacturer complies with all applicable CGMPs.<sup>55</sup> Thus, the implementation by FDA of the 1962 Amendments to the Federal Food, Drug, and Cosmetic Act of 1938 dramatically altered the administrative authority of FDA to regulate the sale and manufacture of drugs. Prior to 1962, a manufacturer could bring to market any drug product by any means of manufacture bearing any therapeutic claims unless FDA could first challenge the product and demonstrate that it was either unsafe or, in the case of labeling, false. After the full implementation of the authority granted to FDA in the 1962 Amendments, no manufacturer could market any drug product unless that product and its active and inactive ingredients and methods of

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<sup>54</sup>28 Fed. Reg. 6,385, now 21 C.F.R. Parts 210, 211. See also Merrill, *supra*, note 16, at 1787.

<sup>55</sup>See Merrill, *supra*, note 16, at 1787 and fn. 105. See e.g. 53 Fed. Reg. 18,905 (1988); 52 Fed. Reg. 7,318 (1987); 52 Fed. Reg. 29,274 (1987).

manufacture, packaging, and labeling were all first approved by FDA as both safe and effective, and then, after this pre-approval, the manufacturer could not make any significant change to the product or its methods of manufacture or labeling without further pre-approval and could not fail to comply with all CGMP procedures for the methods of manufacture of the product.

## **B. Regulation of Biologics**

A “biologic” is any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative... applicable to the prevention, treatment, or cure of diseases.<sup>56</sup> Prior to 1902, the production of vaccines and other biologics was left predominantly unregulated by the federal government.<sup>57</sup> However, in 1901, antitoxin for the treatment of diphtheria produced from a horse infected with tetanus caused the death of thirteen children in St. Louis, Missouri from resulting tetanus infections.<sup>58</sup>

**BIOLOGICS**      The public uproar surrounding this tragedy prompted Congress to adopt the **CONTROL**

**ACT OF 1902**      Biologics Act of 1902 (the 1902 Act).<sup>59</sup>The 1902 Act prohibited the transportation or sale of biologics unless the manufacturer of the biologics had received two separate licenses under the 1902 Act, an Establish-

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<sup>56</sup>42 U.S.C. ♣ 262

<sup>57</sup>In 1813, to deal with the problem of ineffective smallpox vaccines, Congress adopted the Virus Act of 1813, 2 Stat. 806 (1813); however, Congress repealed this Act nine years later, determining that it would be “better to commit the subject altogether to the local authorities” (3 Stat. 677 (1922)). Hutt & Merrill, *supra*, note 2, at 661.

<sup>58</sup>Philip D. Noguchi, M.D., *From Jim to Gene and Beyond: An Odyssey of Biologics Regulation*, 51 FOOD & DRUG L.J. 367, 368 (1996).

<sup>59</sup>Pub.L. No. 244, 32 Stat. 728 *et seq.* (1902).

ment License and a Product License.<sup>60</sup>To obtain an Establishment License, a manufacturer was required to submit an Establishment License Application (ELA) describing the establishment and its facilities and delineating the areas in which the manufacturing processes would take place, and, once an Establishment License was granted, the manufacturing establishment was required to meet continuing “safety” and “purity” guidelines for the methods utilized in the preparation of biologics.<sup>61</sup>An Establishment License could only be granted to a full-scale establishment, and pilot or small-scale manufacturing facilities could not be the subject of an ELA. To obtain a Product License, a manufacturer was required to submit a Product License Application (PLA) describing the manufacturing process, testing, labeling, and packaging of the product, and, once a Product License was granted, each container of biologic product was required to be labeled with the address of the establishment and an expiration date for the product.<sup>62</sup>Once an ELA and PLA were approved, a sample of each lot of a biologic product produced was required to be submitted, along with testing data for that lot, and the manufacturer could not begin distribution of the lot until receiving a written notification of release.<sup>63</sup>Further, any change to either the product or the facility in which that product was manufactured were required to be submitted in a supplemental amended application.<sup>64</sup>

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<sup>60</sup>Biologics Act  $\clubsuit$  1, 32 Stat. at 728.

<sup>61</sup>*Id.* See Hutt & Merrill, *supra*, note 2, at 679.

<sup>62</sup>*Id.* See Hutt & Merrill, *supra*, note 2, at 680.

<sup>63</sup>*Id.*

<sup>64</sup>*Id.*

This system of dual licensing focused upon the methods of manufacture of biologics as a proxy for guaranteeing their safety, and the 1902 Act did not explicitly require manufacturers to demonstrate the efficacy or potency of the actual biologics that they produced. However, as in the drug regulation context, FDA implicitly read such an efficacy and potency into the regulation of biologics under the 1902 Act by mandating in practice that the expiration dating requirement be fulfilled by actual clinical testing of biologics sufficient to demonstrate that the labeling date actually defined a functional effectiveness period, which necessarily required a demonstration of some level of efficacy and potency for any such period to exist.<sup>65</sup> The 1902 Act granted authority to enter and inspect any establishment manufacturing biologics to ensure that the guidelines for safety and purity are in effect.<sup>66</sup> The 1902 Act applies to biologic products intended for use in humans, and Congress has adopted a separate act, the Virus, Serum, and Toxin Act of 1913, to regulate veterinary biologic products; this act is administered by the Animal and Plant Health Inspection Service, a division of the United States Department of Agriculture, and not by FDA.<sup>67</sup>

PUBLIC In 1944, Congress recodified the Biologics Act of 1902 as part  
of the Public HEALTH  
SERVICE Health Service Act of 1944 (the “1944 Act”).<sup>68</sup> As with the 1902  
Act, the 1944 Act ACT OF 1944

focused primarily upon extensive control over the methods of manufacture

<sup>65</sup>Noguchi, *supra*, note 46, at 368.

<sup>66</sup>Biologics Act § 3, 32 Stat. at 729.

<sup>67</sup>Edward L. Korwek, *Human Biological Drug Regulation: Past, Present, and Beyond the Year 2000*, 50 FOOD & DRUG L.J. 123 (1995).

<sup>68</sup>Pub.L. No. 85-410, 58 Stat. 682, 702 (1944), recodified at 42 U.S.C. § 262. *See also* Hutt & Merrill, *supra*, note 2.



of biologics as a proxy for ensuring purity and safety, and the 1994 Act maintained the ELA and PLA license system. However, in the 1944 recodification, Congress explicitly added the requirement that biologics manufacturers demonstrate “potency” as a measure of clinical usefulness.<sup>69</sup> As under the 1902 Act, the 1944 Act granted authority to enter and inspect any establishment manufacturing biologics to ensure that the guidelines for safety and purity are in effect.<sup>70</sup> The 1944 Act also allowed seizure of any biologics that were determined to give rise to a substantial or imminent hazard to the public health.<sup>71</sup> As with drug regulation, the 1944 Act provided for both civil and criminal penalties for violations of its provisions.<sup>72</sup>

CONSUMER Throughout the life of the Public Health Service Act of 1944, Congress vested SAFETY ACT

OF 1972 the administrative authority for regulation of biologics in several separate agencies. Administrative authority was originally granted to the National Biological Institute (NBI) of the National Institutes of Health (NIH). However, in 1955, a contaminated poliomyelitis vaccine produced by Cutter Laboratories was rushed through the NBI approval process and released for general use, which resulted in ten deaths and 192 cases of paralytic polio.<sup>73</sup> As a direct result of this tragedy, administrative authority for the regulation of biologics was transferred by Congress to the Division of Biological Standards (DBS), a newly-

<sup>69</sup>42 U.S.C. § 262. *See also* Noguchi, *supra*, note 46, at 368; Karwaki, *supra*, note 3.

<sup>70</sup>42 U.S.C. § 262(c).

<sup>71</sup>42 U.S.C. § 262(d)(2)(A). *See also* Korwek, *supra*, note 49, at 131.

<sup>72</sup>42 U.S.C. § 262(d)(2)(B) (civil); 42 U.S.C. s 262(f) (criminal). *See also* Cuttler, *supra*, note 27, at 203.

<sup>73</sup>Hutt & Merrill, *supra*, note 2, at 665.

created division of the NIH. DBS was criticized in several highly-publicized articles in the journal *Science* as possessing both an amorphous, decentralized, and often imprecise system for regulating biologics approvals and an inherent conflict of interest in that there often existed several putative strains of vaccine developed to treat a given disease among which DBS must select a single candidate for approval and nationwide distribution, often with one of the several such strains developed by in-house researchers at DBS.<sup>74</sup> Amid this criticism, an investigation of DBS conducted by the General Accounting Office (GAO) reported that, according to DBS records, 130 of the 221 total lots<sup>75</sup> of influenza vaccine approved by DBS between 1966 and 1968 failed to meet the regulatory standards for potency set by DBS itself.<sup>76</sup> GAO also found that DBS was consistently not applying the efficacy standards of the Drug Amendments of 1962 to biologic products. This GAO report, and subsequent hearings before the Senate Subcommittee on Executive Reorganization and Government Research, lead Congress to adopt the Consumer Safety Act of 1972, which transferred regulatory authority for the administration of the 1944 Act from NIH to FDA.<sup>77</sup> To administer the requirements of the 1944 Act, FDA formed the Bureau of Biologics.

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<sup>74</sup>Hutt & Merrill, *supra*, note 2, at 666-7, citing Wade, *Division of Biologics Standards: Scientific Management Questioned*, 175 *Science* 996 (1972).

<sup>75</sup>221 lots is approximately 67 million individual doses. Hutt & Merrill, *supra*, note 2, at 668.

<sup>76</sup>Hutt & Merrill, *supra*, note 2, at 668, citing Wade, *DBS: Agency Contravenes Its Own Regulations*, 176 *Science* 34 (1972).

<sup>77</sup>Hutt & Merrill, *supra*, note 2, at 668, citing *Hearings before the Senate Subcommittee on Executive Reorganization and Government Research of the Senate Committee on Government Operations*, 92d Cong., 2d Sess. (1972). *See also* 37 Fed.Reg. 12,865 (June 29, 1975).

Prior to 1972, regulation of biologics under NIH had focused primarily upon the Public Health Service Act of 1944 and its requirements of safety, purity, and potency, however, once administrative responsibility for the regulation of biologics shifted from NIH to FDA, FDA announced its intention to require that all new biologic products satisfy the additional standards of safety and efficacy mandated in the Drug Amendments of 1962, relying in large part upon its authority under the misbranding provisions of the 1944 Act.<sup>78</sup> Biologics, therefore, were to be required to meet safety, purity, potency, and efficacy standards prior to FDA approval.<sup>79</sup> Although this expansive reading of the misbranding provisions of the 1944 Act seemed at first blush to have greatly expanded the evidentiary burdens placed upon biologics manufacturers, it should be noted that, because the definition of a “drug” under the 1938 Act turns largely upon the intended use of the product, the majority of biologic products actually fall under the coverage of the 1938 Act.<sup>80</sup>

In an even more controversial exercise of its administrative authority, FDA

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<sup>78</sup>21 C.F.R. ♣ 601.25. See also *Biological Products: Procedures for Review of Safety, Effectiveness and Labeling*, 38 Fed.Reg. 4319 (February 13, 1973) (proposed in 37 Fed.Reg. 16,679 (August 18, 1972)):

“Regardless of whether a particular biological product is a new drug, however, all biological products are subject to the misbranding provisions of both section 502 of the Federal Food, Drug, and Cosmetic Act and section 351(b) of the Public Health Service Act. A biological product whose label purports, represents, or suggest it to be effective and/or safe for certain intended uses, and which is not safe and effective for such uses, is misbranded within the meaning of both acts, and therefore should not and will not be licensed under section 351 of the Public Health Service Act.”

See also, Hutt and Merrill, *supra*, note 2, at 671; Korwek, *supra*, note 49, at 131.

<sup>79</sup>See Korwek, *supra*, note 49, at 126.

<sup>80</sup>Federal Food, Drug, and Cosmetics Act ♣201(g), 52 Stat. 728, 1041, codified as amended at 21 U.S.C. ♣ 321(g)(1)(B): A product used in interstate commerce will constitute a “drug” under the 1938 Act if it is “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals or . . . intended to affect the structure or any function of the body of man or other animals.”

further announced its intention to apply the safety and efficacy provisions of the 1962 Amendments to all biologics that had already received prior approval from NIH and to insist that all such prior-approved biologics additionally demonstrate safety and efficacy.<sup>81</sup>FDA implemented this process, referred to as the “Biologics Review”, by defining multiple categories of biologics to be reexamined, issuing requests for data from manufacturers of biologic products approved in each such category, and appointing multiple advisory review panels to make recommendations to FDA regarding the safety and efficacy of the reexamined biologics.<sup>82</sup>The cross-application of the Public Health Service Act of 1944 and the Federal Food, Drug, and Cosmetics Act of 1938 to products of biotechnology highlights some of the key differences in the FDA regulatory schemes for drugs and biologics, as it makes the requirements and enforcement powers of each regulatory scheme applicable to a cross-regulated product. Biologics are subject to license requirements, whereas drugs must be the subject of a pre-approved NDA. Thus, even a fully-licensed establishment must delay production of a product until the clinical trials process is complete and an NDA is approved by FDA. Additionally, once an ELA license is granted, any change in the method of manufacture of the product is presumed to adversely effect the safety, purity, and potency of the product, though this would not be the case for a product regulated solely as a drug. Because of this presumption, FDA has

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<sup>81</sup>See Food and Drug Administration, *Biological Products: Procedures for Review of Safety, Effectiveness, and Labeling*, 37 Fed.Reg. 16,679 (1972). See also Hutt & Merrill, *supra*, note 2, at 669.

<sup>82</sup>*Id.*

traditionally insisted that there could not be an approved generic version of a biologic product, which also makes the protections of the Drug Price Competition and Patent Term Restoration Act of 1984, discussed below, inapplicable to biologic drug products.<sup>83</sup> Further, FDA originally interpreted the ELA and PLA provisions to require the same legal entity to hold both licenses, thus even a product with a fully-approved NDA could only be produced at a fully-licensed manufacturing establishment.<sup>84</sup> Also, biological products were subject to seizure if FDA determines that a substantial or imminent risk to the public health exists, whereas products regulated solely as drugs would not be subject to seizure unless the products were adulterated or misbranded.<sup>85</sup>

### C. Regulation of Medical Devices

In contrast to the regulation of drugs and biologics, both of which have been actively regulated for nearly a century, the regulation of medical devices is much more recent. Though FDA has actually possessed authority to review and regulate medical devices since 1938, the FDA did not at that time possess pre-approval authority over medical devices, and thus FDA was required to challenge individual device manufacturers in court.

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<sup>83</sup>Pub. L. No. 98-417, 98 Stat. 1585 (1984), codified at 15 U.S.C. §§ 68b-c, 70b; 21 U.S.C. §§ 301, 28 U.S.C. § 2201, and 35 U.S.C. §§ 156, 271, 282; *see infra*. *See also* Korwek, *supra*, note 49, at 126. FDA announced its determination of the inapplicability of the Drug Price Competition and Patent Term Restoration Act of 1984 to generic biologic products in 57 Fed. Reg. 17,950, 17,951 (1992).

<sup>84</sup>*See* 21 C.F.R. § 601.10(b).

<sup>85</sup>*See* 42 U.S.C. § 262(d)(2)(A) (seizure of biologics); 21 U.S.C. § 374(a), (c), and (d) (seizure of drugs), both codified as amended.

Prior to 1938, there existed a significant number of machines and instruments claimed to possess beneficial medical properties or to assist in the treatment of diseases, however, the majority of doctors and scientists at that time believed that nearly all such claims were fraudulent or at best unsubstantiated.<sup>86</sup>

FEDERAL In order to deal with the perceived threat of potential public  
injury resulting COSMETICS  
ACT OF 1938 from ineffective or unsafe medical devices, Congress first granted  
FDA authority FOOD, DRUG

AND to regulate medical devices under the Federal Food, Drug, and Cos-  
metic Act of 1938 (the “1938 Act”),<sup>87</sup>The 1938 Act defined “devices” as all  
“instruments, apparatus, and contrivances. . .intended (1) for use in the diag-  
nosis, cure, mitigation, treatment, or prevention of disease in man or other  
animals; or (2) to affect the structure or any function of the body of man or  
other animals.”<sup>88</sup> As with the definition of “drug” under the 1938 Act, the defi-  
nition of “device” turned largely upon the intended use of the product, and thus  
most instruments intended for use in medical care fell within this broad defi-  
nition.<sup>89</sup> While the majority of medical machines and instruments existing in  
1938 fell within this definition of a “device”, the 1938 Act granted to FDA only  
the limited authority to challenge medical devices that were “misbranded” or  
“adulterated.”<sup>90</sup>This limitation meant that FDA could not implement a system  
of pre-market approval, as it had with drugs, or require that device manufac-

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<sup>86</sup>Merrill, *supra*, note 16, at 1802.

<sup>87</sup>52 Stat 1040, Ch. 675, codified as amended at 21 U.S.C. ♣ 301 *et seq.* (June 25, 1938).

<sup>88</sup>Federal Food, Drug, and Cosmetics Act ♣201(h), 52 Stat. at 1041.

<sup>89</sup>*See* Merrill, *supra*, note 16, at 1,801.

<sup>90</sup>Federal Food, Drug, and Cosmetics Act ♣301, 52 Stat. at 1042.

turers demonstrate either the safety or the efficacy of their products. While FDA did successfully challenge a large number of devices marketed with fraudulent claims, often these devices merely reappeared with a new set of medical claims.<sup>91</sup> Thus, the 1938 Act did not provide FDA with the authority necessary to fully regulate medical devices.

DRUG                      Following the Thalidomide tragedy in 1957, FDA proposed legislation to AMENDMENTS

OF 1962      Congress that would grant FDA pre-market approval authority over medical devices.<sup>92</sup> However, as a result of political compromises in Congress, FDA abandoned this proposal in order to ensure the adoption of the Drug Amendments of 1962.<sup>93</sup> While this compromise left FDA in its original position of lacking adequate authority to fully regulate medical devices, the 1962 Amendments greatly increased FDA authority over drugs. The 1960's, however, saw an explosion in the number and complexity of new medical devices, such as pacemakers, heart valves, and kidney dialysis machines.<sup>94</sup> Because of the complexity and wide-spread use of such devices, as well as an increasing number of deaths, infections, and manufacturer recalls resulting from unsafe or defective devices, FDA believed that many such medical devices posed a significant risk to the public health, yet, because of the compromises surrounding the adoption of the Drug Amendments of 1962, FDA did not possess the pre-market approval

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<sup>91</sup>Merrill, *supra*, note 16, at 1803, citing Hutt & Merrill, *supra*, note 2, at 736-37.

<sup>92</sup>Peter Barton Hutt, *A History of Government Regulation of Adulteration and Misbranding of Medical Devices*, 44 F.D.C. L.J. 99, 101-05 (1989). See also Merrill, *supra*, note 16, at 1804.

<sup>93</sup>*Id.*

<sup>94</sup>For a more extensive list of medical devices developed in the 1960's, see Hutt & Merrill, *supra*, note 2, at 742-3.

authority it believed necessary to sufficiently regulate devices.<sup>95</sup> To overcome this lack of pre-market approval authority, FDA began to leverage its newfound drug authority to bolster the strength of its medical device regulation. FDA utilized the expansive definition of the term “drug” in order to classify some medical devices as “drugs”, thereby allowing FDA to require both pre-market approval and a demonstration of the efficacy of the device. When medical device manufacturers challenged FDA in court, FDA again found an ally in the Supreme Court, which upheld this tactic of reclassification of certain medical devices as drugs, as the Supreme Court had approved FDA’s other expansive implementations of the 1962 Amendments in the drug context.<sup>96</sup> Mirroring the Supreme Court’s support for the expansion of FDA authority over medical devices, President Nixon ordered the Department of Health, Education, and Welfare (HEW) to conduct a study of medical devices, publish a report of its findings, and propose legislative reforms, if necessary, to medical device regulation under the Federal Food, Drug, and Cosmetics Act of 1938 for submission to Congress.<sup>97</sup> To carry out President Nixon’s directive, HEW appointed Theodore Cooper, then Director of the Heart and Lung Institute, to head a study group (commonly called the “Cooper Committee”) to conduct this medical device research.<sup>98</sup> The Cooper Committee issued its report in September

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<sup>95</sup>For several examples of 1960’s medical devices that resulted in injuries, deaths, and manufacturer recalls, see Hutt & Merrill, *supra*, note 2, at 743.

<sup>96</sup>*United States v. An Article of Drug... Bacto-Unidisk...*, 394 U.S. 784 (1969). Larry R. Pilot & Daniel R. Waldmann, *Food and Drug Administration Modernization Act of 1997: Medical Device Provisions*, 53 FOOD & DRUG L.J. 267, 268 (1998). See also Merrill, *supra*, note 16, at 1805; Hutt & Merrill, *supra*, note 2, at 731.

<sup>97</sup>President Richard Nixon, Consumer Message to Congress (1969). Pilot & Waldmann, *supra*, note 76, at 268. See also Hutt & Merrill, *supra*, note 2, at 743.

<sup>98</sup>*Id.*



1970.<sup>99</sup>

DEVICE As a direct result of this report (referred to as the “Cooper Committee AMENDMENTS

OF 1976 Report”), Congress ultimately passed the Device Amendments of 1976 (the “1976 Amendments”), which amended the 1938 Act.<sup>100</sup> The 1976 Amendments revised the definition of the term “device” to include any “instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article. . . . which does not achieve any of its principal 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 any of its principal intended purposes.”<sup>101</sup> Congress intended this definition to be broad enough to encompass both devices formerly classified as “drugs” by FDA prior to the adoption of the 1976 Amendments and devices intended to diagnose and treat purely physiological conditions not normally regarded as diseases, such as pregnancy.<sup>102</sup> This broad definition made all such covered devices subject to the general provisions of the 1938 Act, including adulteration and misbranding regulations, Good Manufacturing Practice guidelines, limited establishment registration requirements, recordation and reporting requirements, and seizure, inspection, and recall enforcement authority.<sup>103</sup>

<sup>99</sup>Department of Health, Education, and Welfare, Study Group on Medical Devices, *Medical Devices: A Legislative Plan* (September 1970). See also Pilot & Waldmann, *supra*, note 76, at 268; Hutt & Merrill, *supra*, note 2, at 743.

<sup>100</sup>Pub.L. No. 94-95, 90 Stat. 539, codified in various parts of 21 U.S.C. (May 28, 1976).

<sup>101</sup>Device Amendments ♣ 3(a)(1)(A), 90 Stat. at 575.

<sup>102</sup>Hutt & Merrill, *supra*, note 2, at 745.

<sup>103</sup>Codified severally in 21 C.F.R. Part 807 (establishment registration), 21 C.F.R. Part 820 (good manufacturing practices), 21 C.F.R. Part 803 (recordation and reporting), Federal Food, Drug, and Cosmetics Act ♣ 518 (seizure, repair, and recall).

The central thesis of the Cooper Committee Report had been that medical devices were too diverse to allow a uniform system of regulation and that medical devices instead should be grouped into categories possessing increasingly stringent regulatory requirements based upon the potential risks to public safety and health posed by the various medical devices; the 1976 Amendments drew upon this thesis by requiring FDA to categorize all existing medical devices into three separate regulatory classes.<sup>104</sup> Medical devices of low risk to the public health for which FDA determined that the general regulatory controls for devices were “sufficient to provide reasonable assurance of the safety and effectiveness of the device” were categorized as Class I Devices under the 1976 Act and were subject only to the general regulatory scheme of the 1938 Act existing prior to the 1976 Amendments, namely regulation of misbranding and adulteration.<sup>105</sup> Medical devices for which FDA believed that mere misbranding and adulteration controls were not adequate to ensure the public health were categorized either as Class II Devices if sufficient information existed to enable FDA to issue performance and design standards for the manufacture of such devices or as Class III Devices if existing information was insufficient to allow FDA to establish such manufacturing standards.<sup>106</sup> Class II devices were subject to categorical performance and manufacturing guidelines prescribing the functional features and characteristics of all products of that type, whereas Class III devices were

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<sup>104</sup>Device Amendments ♣ 513, 90 Stat. at 540-2. *See also Merrill, supra*, note 16, at 1,807.

<sup>105</sup>Device Amendments ♣ 513(a)(1)(A), 90 Stat. at 540. *See also Hutt & Merrill, supra*, note 2, at 745.

<sup>106</sup>Device Amendments ♣ 513(a)(1)(B), 90 Stat. at 541 (Class II); Device Amendments ♣ 513(a)(1)(C), 90 Stat. at 541 (Class III). *See also Hutt & Merrill, supra*, note 2, at 745.

subject to pre-market review for safety and efficacy, similar to the review of new drugs.<sup>107</sup> All new medical devices introduced subsequent to the adoption of the 1976 Amendments were to be classified as Class III Devices unless and until the manufacturer could convince FDA to reclassify the new device.<sup>108</sup> Additionally, all devices categorized by FDA as “drugs” prior to the adoption of the 1976 Amendments were to be categorized as Class III devices.<sup>109</sup>

The pre-market approval process for Class III medical devices under the Device Amendments of 1976 mirrors the analogous pre-market approval process for drugs under Drug Amendments of 1962, with several notable differences. The 1976 Amendments prohibit the transportation in interstate commerce of unapproved Class III medical devices unless such devices are subject to an “Investigational Device Exemption” (IDE).<sup>110</sup> The IDE is the functional equivalent of the Investigational New Drug application, except that FDA will accept IDEs based upon proposed Product Development Protocols that have been approved by local institutional review boards if FDA determines that the device to be tested does not pose a “significant risk” to public health.<sup>111</sup> Once clinical testing is complete, the manufacturer of a device must file a Pre-Market Approval (PMA) application with FDA, containing full and complete reports of all clinical research conducted by the device manufacturer, in order to demonstrate the

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<sup>107</sup>Merrill, *supra*, note 16, at 1,809.

<sup>108</sup>Device Amendments ♣ 513(e). *See also* 42 Fed.Reg. 63,472 (December 16, 1977).

<sup>109</sup>Device Amendments ♣ 513(e); Federal Food, Drug, and Cosmetics Act ♣ 520(l)(2). *See also* 42 Fed.Reg. 63,472 (December 16, 1977).

<sup>110</sup>Device Amendments ♣ 520(g), 41 Fed.Reg. 35,282 (August 20, 1976), 43 Fed.Reg. 20,726 (May 12, 1978), 43 Fed.Reg. 25,142 (June 9, 1978), 45 Fed.Reg. 3,732 (January 18, 1980); Hutt & Merrill, *supra*, note 2, at 756.

<sup>111</sup>Device Amendments ♣ 520(g), 45 Fed.Reg. 6,255 (September 19, 1980).

safety and efficacy of the device.<sup>112</sup> In contrast to the NDA approval process, the 1976 Amendments require FDA to consult with advisory committees prior to approval of a PMA; in practice, FDA actually submits many drug NDAs to similar advisory committees as well, however, this practice in the drug context is purely voluntary on the part of FDA.<sup>113</sup>

Although a large number of new and existing medical devices were categorized as Class III devices under the regulatory system created by the 1976 Amendments, and thereby subjected to extensive pre-market approval requirements, the 1976 Amendments allowed two methods that manufacturers could utilize to reclassify a medical device as Class I or II, thereby avoiding pre-market approval bars to immediate marketing of the reclassified medical devices. First, any new medical device that was “substantially equivalent” to a medical device marketed prior to the adoption of the 1976 Amendments was reclassified to the same Class as the pre-1976 “predicate” device, thus allowing the reclassification of the device to avoid pre-market approval and requiring the reclassified device only to meet the performance and manufacturing standards (if any) set for the group of devices into which the pre-1976 “predicate” device was categorized.<sup>114</sup> To utilize the “substantial equivalent” reclassification scheme (contained in section 510(k) of the 1976 Amendments, and thus commonly referred to as the “510(k) process”), at least ninety days prior to a manufacturer’s intended date of market intro-

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<sup>112</sup>Device Amendments ♣ 515, 45 Fed.Reg. 81,769 (Dec.12, 1980), 51 Fed.Reg. 26,342 (July 22, 1986), codified in 21 C.F.R. Part 814.

<sup>113</sup>Federal Food, Drug, and Cosmetics Act ♣ 513(a)(2)-(3), codified at 21 U.S.C. ♣ 360c(a)(2)-(3) (1994). See Merrill, *supra*, note 16, at 1,821.

<sup>114</sup>Federal Food, Drug, and Cosmetics Act ♣510(k), as amended; Merrill, *supra*, note 16, at 1,811.

duction of a new medical device, the manufacturer was required to notify FDA both of its intention to so introduce the new medical device into the market and of its reasons for concluding that the new device was substantially equivalent to the pre-1976 predicate device.<sup>115</sup>This ninety-day notice requirement (referred to as a “pre-market notification”) provided FDA with a limited pre-market review period in which to decide whether to accept the manufacturer’s rationale for equivalence or instead to conclude that the medical device possessed unique features, properties, or uses sufficient to require full pre-market review of the medical device prior to marketing.<sup>116</sup>FDA further liberalized this reclassification process by allowing manufacturers to claim substantial equivalence to devices marketed after 1976 if such post-1976 device themselves had claimed a pre-1976 device as a “predicate” for reclassification.<sup>117</sup>This second opportunity for reclassification, commonly called “piggybacking”, provided an ever-broadening method for the reclassification of new medical devices.<sup>118</sup> Indeed, the existence of such expansive opportunities for exemption from the pre-market approval requirement for devices, coupled with the fact that FDA did not propose a single set of performance and manufacturing standards for Class II Devices for more than a decade after the adoption of the 1976 Amendments, served to substan-

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<sup>115</sup>Federal Food, Drug, and Cosmetics Act ♣ 510(k) (codified as amended at 21 U.S.C. ♣ 360(k) (1994)); Merrill, *supra*, note 16, at 1,811.

<sup>116</sup>21 C.F.R. ♣807.81 *et seq.*, 41 Fed.Reg. 37,485 (September 3, 1976), 42 Fed.Reg. 42,520 (August 23, 1977). *See* Hutt & Merrill, *supra*, note 2, at 755. *See also* FDA, *Guidance on the Center for Devices and Radiological Health’s Pre-market Notification Review Program* (June 30, 1986).

<sup>117</sup>Merrill, *supra*, note 16, at 1,811, citing Letter from D. Bruce Burlington, Director, Center for Devices and Radiological Health, Food and Drug Administration, to Presidents or Chief Executive Officers, Medical Device Manufacturing Companies (Nov. 1, 1995).

<sup>118</sup>*Id.*

tially mitigate the effect of the adoption of the 1976 Amendments on device manufacturers.<sup>119</sup>

The 1976 Amendments also contained provisions that prohibited states from adopting regulations “different from, or in addition to, any requirements under this Act”; while this state preemption went largely unnoticed when passed, it would play a significant role two decades later in shielding device manufacturers that had plead guilty to violations of FDA regulations from state civil tort suits which alleged *per se* negligence arising from such violations.<sup>120</sup>

Thus, the Device Amendments of 1976 provided FDA with the administrative power necessary to build the modern system of device regulation. The 1976 Amendments also introduced the concepts of product classifications, utilization of institutional review boards, and consultation of expert advisory committees.

#### **D. Regulation of Foods**

PURE FOOD AND DRUGS ACT OF 1906 Congress first granted FDA authority to regulate foods in the Pure Food and AND DRUGS

ACT OF 1906 Drugs Act of 1906 (the “1906 Act”).<sup>121</sup> The 1906 Act provides for both civil and criminal penalties for violation of its provisions.<sup>122</sup>

The 1906 Act prohibits the introduction, delivery, or receipt of any adulterated or misbranded food in interstate commerce. The 1906 Act defined “food” as

<sup>119</sup> See Merrill, *supra*, note 16, at 1816.

<sup>120</sup> Jeffery N. Gibbs, *The Human Genome, FDA and Product Liability*, 7 RISK: HEALTH SAFETY & ENV'T 267, 275 (Summer 1996).

<sup>121</sup> 34 Stat. 728 (June 30, 1906) (repealed in 1938).

<sup>122</sup> Pure Food and Drugs Act § 1, 34 Stat. at 728.

“all articles used for food, drink, confectionery, or condiment by man or other animals, whether simple, mixed, or compound.”<sup>123</sup> The 1906 Act stated that a food is “adulterated” if (1) “any substance has been mixed and packed with it so as to reduce or lower or injuriously affect its quality or strength”, (2) “if any substance has been substituted wholly or in part for the article”, (3) “if any valuable constituent of the article has been wholly or in part abstracted”, (4) “if it be mixed, colored, powdered, coated, or stained in a manner whereby damage or inferiority is concealed”, or (5) “if it contain any added poisonous or other added deleterious ingredient which may render such article injurious to health”.<sup>124</sup> The 1906 Act defines a food as “misbranded” if (1) “it be an imitation of or offered for sale under the name of another article”, (2) “it be labeled or branded so as to deceive or mislead the purchaser”, (3) “the contents of the package. . . have been removed. . . and other contents shall have been placed in such package”, (4) “it fail to bear a statement on the label of the quantity or proportion of [certain enumerated substances]”, or (5) if the label bears any incorrect statement regarding “weight or measure” or any false or misleading “statement, design, or device”.<sup>125</sup> The definition of “misbranded” was later amended by Congress in 1913 to require food labeling to describe the contents “in terms of weight, measure, or numerical count.”<sup>126</sup>

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<sup>123</sup>21 U.S.C. § 321(f).

<sup>124</sup>Pure Food and Drugs Act § 7, 34 Stat. at 770, codified as amended at 21 U.S.C. s 342(a).

<sup>125</sup>Pure Food and Drugs Act § 8, 34 Stat. at 770-1. ). The enumerated substances that were required to be disclosed in the labeling were “alcohol, morphine, opium, cocaine, heroin, alpha or beta eucaine, chloroform, cannabis indica, chloral hydrate, or acetanilide, or any derivative or preparation of any such substances”. *Id.*

<sup>126</sup>37 Stat. 732 (1913). *See also* Hutt and Hutt II, *A History of Government Regulation of Adulteration and Misbranding of Food*, 39 F.D.C. L.J. 2, 58 (1984).

Although the broad definition of “food” under the Pure Food and Drugs Act of 1906 granted FDA extensive authority over nearly all types of food, several specific categories of foods are regulated under additional Acts as well.<sup>127</sup> Meat, poultry, and eggs are regulated under the Federal Meat Inspection Acts of 1906 and 1907, the Poultry Products Inspection Act of 1957, and the Egg Products Inspection Act of 1970.<sup>128</sup> Most alcoholic beverages are regulated by the Bureau of Alcohol, Tobacco, and Firearms under the Federal Alcohol Administration Act of 1935, though FDA also regulates alcoholic products as foods.<sup>129</sup> While the 1906 Act gave FDA significant authority to regulate foods, it possessed several shortcomings. First, the 1906 Act did not grant FDA authority to inspect food manufacturing establishments.<sup>130</sup> Additionally, FDA could only enforce the misbranding provisions of the 1906 Act against claims made in the label of foods.<sup>131</sup> The 1906 Act also did not adequately deal with products that merely possessed ingredients of inferior quality or quantity without any affirmatively misleading statement in its labeling, which has been termed “economic adulteration”.<sup>132</sup> While the 1906 Act had granted USDA authority to establish food standards for purity and content, FDA began to insist that adequate enforcement of food regulations was not possible without the authority

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<sup>127</sup> See generally J. H. Maryanski, *FDA's Policy for Foods Developed by Biotechnology*, Center for Food Safety and Applied Nutrition Handout: 1995, AMERICAN CHEMICAL SOCIETY SYMPOSIUM SERIES No. 605 (1995) (Available on-line)

<sup>128</sup> 21 U.S.C. §601 *et seq.*, 21 U.S.C. §451 *et seq.*, and 21 U.S.C. §1013 *et seq.*, respectively. See also, Hutt & Merrill, *supra*, note 2, at 34 (“USDA has ceded to FDA jurisdiction over any food containing less than two percent of meat or poultry. The jurisdiction of USDA and FDA over these three categories of food products is otherwise complex and uncertain.”).

<sup>129</sup> 49 Stat. 977 (1935). See Hutt & Merrill, *supra*, note 2, at 34-35.

<sup>130</sup> Hutt & Hutt II, *supra*, note 104, at 61.

<sup>131</sup> See Pure Food and Drugs Act § 8, 34 Stat. at 770-1.

<sup>132</sup> Hutt & Hutt II, *supra*, note 104, at 63.



to establish mandatory standards of identity and quality of ingredients, as well as mandatory requirements for the contents of food labeling.<sup>133</sup>

FEDERAL To overcome these inadequacies in the regulation of foods under the Pure Food FOOD, DRUG, AND and Drugs Act of 1906, Congress included food regulation reforms in the Federal Food, COSMETICS

ACT OF 1938 Drug, and Cosmetic Act of 1938 (the “1938 Act”), which repealed the 1906 Act.<sup>134</sup> The 1938 Act granted FDA’s request for administrative authority to mandate standards for food identity and quality, limited only by the requirement that such standards be reasonably tailored to promote “honesty and fair dealing in the interest of consumers.”<sup>135</sup> This grant gave FDA nearly unbounded authority to control the content of foods, and FDA utilized this authority to hold illegal, whether by “adulteration” or “misbranding”, any food that did not conform to FDA food standards.<sup>136</sup> The Supreme Court upheld FDA’s extensive use of such food standards to define adulteration and misbranding in 1943, however, the Court held that a product not conforming to FDA’s standards for ingredients could be marketed so long as it bore labeling indicating that it was an “imitation” product.<sup>137</sup> In addition, whereas the 1906 Act considered only foods with exogenous toxic substances to be adulterated, the 1938 Act gave FDA the authority to seize foods that contained both endogenous and exogenous toxic substances that would render the food injurious

<sup>133</sup>See FDA, *Annual Report, 1933*, Food Law Institute, Federal Food, Drug and Cosmetic Law Administrative Reports 1907-1949, at 13-16 (1933).

<sup>134</sup>See *infra* note 18. See also Michele J. Brace, *Regulation of Genetically Engineered Foods Under the Federal Food, Drug, and Cosmetic Act*, 33 AM. U.L. REV. 899, 902 (Summer 1984).

<sup>135</sup>Federal Food, Drug, and Cosmetics Act ♣ 401, 52 Stat. at 1046.

<sup>136</sup>Hutt & Hutt II, *supra*, note 104, at 65.

<sup>137</sup>*Federal Security Administrator v. Quaker Oats Co.*, 318 U.S. 218 (1943).

to the public health.<sup>138</sup>

The 1938 Act also required mandatory disclosures in the labeling of all foods; food labels were required to contain the name and address of the manufacturer, the net quantity of the contents, a statement of the ingredients, and the name of the food; disclosure of this information was not required under the 1906 Act.<sup>139</sup> FDA would later utilize the requirement that all foods labels bear the name of the food in order to further extend its control over food contents and identity, by prescribing requirements for the content of certain named foods and holding misbranded all foods so labeled that did not meet these content requirements.<sup>140</sup> This name-based requirements approach of FDA was upheld when challenged in court.<sup>141</sup>

FOOD While the Federal Food, Drug, and Cosmetics Act of 1938 granted FDA pre-AMENDMENT market approval power for the regulation of drugs, it did not grant FDA pre-market OF 1958

approval power over foods, but merely the post-market enforcement power to seize adulterated or misbranded foods. However, twenty years after the adoption of the 1938 Act, Congress once again expanded the regulatory authority of FDA over foods in the Food Additives Amendment of 1958 (the “1958 Amendment”),

<sup>138</sup>Federal Food, Drug, and Cosmetics Act § 402(a), 52 Stat. at 1046, codified as amended at 21 U.S.C. § 342(a)(1). See Brace, *supra*, note 111, at 905-906. See also *United States v. Lexington Mill & Elevator Co.*, 232 U.S. 399 (1914) (finding that “adulteration” under the 1906 Act required a showing of an injurious quantity of the toxic substance present in the food, and not merely the presence of the toxic substance).

<sup>139</sup>Federal Food, Drug, and Cosmetics Act § 403, 52 Stat. at 1047. See Hutt & Hutt II, *supra*, note 104, at 67.

<sup>140</sup>See 37 Fed.Reg. 12,327 (June 22, 1972); 38 Fed.Reg. 6,964 (Mar. 14, 1973); 21 C.F.R. Part 102; Hutt & Hutt II, *supra*, at 69.

<sup>141</sup>*American Frozen Food Institute v. Califano*, 555 F.2d 1,059 (D.C. Cir. 1977).

which granted FDA pre-market approval power over all food additives.<sup>142</sup> The 1958 Amendment adopted the “generally recognized as safe” approach of the 1938 Act, defining a “food additive” as all exogenous substances added to food that are not “generally recognized as safe” for human consumption.<sup>143</sup> All foods containing unapproved food additives were considered “adulterated” and thereby subject to seizure.<sup>144</sup> All food substances that had been approved by FDA prior to 1958 were grandfathered under the 1958 Amendments and exempted from the definition of a “food additive”.<sup>145</sup> As with the treatment of “me-too” drugs under the 1938 Act, approval by FDA of a food additive as “generally recognized as safe” meant that all food producers could use that food additive without pre-market approval from FDA.<sup>146</sup>

### **III. The Struggle for Form: Asilomar and Uncertainty (1973-1983)**

The first three-quarters of the twentieth century saw a dramatic increase in the extent and strength of FDA administrative authority to regulate drugs, biologics, devices, and foods. Where such authority was unsettled, inadequate, and often non-existent at the dawn of the century, by the late 1970s, FDA possessed the authority necessary to build its system of four strong, though highly variable, regulatory frameworks designed to safeguard the public health against unsafe, ineffectual, and unsuitable drugs, biologics, devices, and foods. In de-

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<sup>142</sup>Pub. L. No. 85-929, 72 Stat. 1,784 (1958), codified at 21 U.S.C. ♣ 348 (1982). See Brace, *supra*, note 111, at 907.

<sup>143</sup>21 U.S.C. ♣ 321(s) (1982).

<sup>144</sup>21 U.S.C. ♣ 348(a) (1982).

<sup>145</sup>21 U.S.C. ♣ 321(s)(4) (1982).

<sup>146</sup>See Brace, *supra*, note 112, at 907.

termining within which administrative framework(s) the new product would be regulated, however, this FDA system looked primarily to the intended use to which a manufacturer planned to put a new product and all but ignored the process of development and method of manufacture of a new product. It was against this regulatory backdrop that a revolutionary new method for the development and manufacture of new products emerged that would test the stability and practical limitations of the FDA regulatory system.

For the first time, in 1973, two scientists inserted a gene from an animal, a toad, into a bacterium and successfully caused this toad gene to function inside the bacterium. This experiment marked the beginning of the era of recombinant genetics and biotechnology. The results of these experiments were presented to colleagues at the Gordon Research Conference on Nucleic Acids in July of 1973. In response to the announcement of the success of these experiments, and their shocking implications, the scientists in attendance at this conference, a group of the most prominent academic biologists, co-authored a letter to Dr. Philip Handler, President of the National Academy of Sciences (NAS), and Dr. John Hogness, President of the Institute of Medicine, NAS, requesting that all research into the new field of recombinant genetics be subject to government regulation, that there be a moratorium on all such research until an international conference could be called to assess the potential hazards that could result from recombinant technology, and that NIH establish a committee to provide advice and establish guidelines for such research. This letter was later published

in the journal *Science*.<sup>147</sup> The publication of this letter focused immense public attention and debate on the correct method for controlling biotechnology.

In response to this public attention, the National Institutes of Health (NIH) established the Recombinant DNA Advisory Committee (RAC) in 1974 to oversee research in recombinant technology.<sup>148</sup> NIH directed RAC to formulate guidelines, to be released by NIH, for the conduct of research in recombinant genetics. In 1975, following the suggestion of the *Science* co-authors, an international conference was held at the Asilomar Conference Center in Pacific Grove, California, to consider the implications of recombinant genetics. The scientific consensus of the Asilomar conference, published in the 1975 Summary Statement of the Asilomar Conference on Recombinant DNA Molecules<sup>149</sup> (the “1975 Statement”), was that only a few types of genetic experiments should not be performed and that the vast majority of research could continue under appropriate physical and biological safeguards.<sup>150</sup> The 1975 Statement called upon NIH to issue guidelines to implement the suggestions of the Asilomar conference.<sup>151</sup> At the first meeting of RAC, held in San Francisco shortly after the Asilomar conference, RAC

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<sup>147</sup>Berg, Baltimore, Boyer, Cohen, Davis, Hogness, Nathans, Roblin, Watson, Weissman & Zinder, *Potential Biohazards of Recombinant DNA Molecules*, 181 *SCIENCE* 1114 (1973) (hereinafter Berg *et al.*). See also Valerie M. Fogleman, *Regulating Science: An Evaluation of the Regulation of Biotechnology Research*, 17 *ENVTL. L.* 183 (Winter 1987).

<sup>148</sup>RAC possesses authority to regulate only recombinant DNA technology, which requires two pieces of DNA spliced—or recombined—outside of a living organism. National Institutes of Health, Recombinant DNA Advisory Committee; Meeting, 49 *Fed. Reg.* 696, 697 (1984). See Fogleman, *supra*, note 125, at 206.

<sup>149</sup>1975 *Summary Statement of the Asilomar Conference on Recombinant DNA Molecules* 188 *SCIENCE* 991 (1975), 225 *NATURE* 442 (1975), 72 *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES* 1981 (1975).

<sup>150</sup>See Donald S. Fredrickson, Director, NIH, *Introductory Statement to the Recombinant DNA Research Guidelines*, 41 *Fed. Reg.* 27,902, 27,902 (1976).

<sup>151</sup>*Id.*

proposed that NIH follow the suggestion of the Asilomar conference members and base the NIH guidelines for genetic research upon the recommendations contained in the 1975 Statement.<sup>152</sup>

NIH In 1976, NIH released the NIH Recombinant DNA Research Guidelines (the RECOMBINANT DNA “NIH Guidelines”), which set out mandatory research protocols and limitations for all RESEARCH GUIDELINES research institutions receiving NIH funding to conduct research in recombinant (1976)

genetics.<sup>153</sup>The NIH Guidelines implemented the suggestions of the 1975 Statement, as RAC had suggested. The NIH Guidelines prohibited several categories of genetic experimentation, including the unauthorized release of all genetically-altered organisms, defined physical and biological containment procedures for sets of genetic research protocols, defined in detail the responsibilities and liabilities of all members of a research team and sponsor organization, and mandated the formation of an Institutional Biosafety Committee (IBC) at every research institution receiving NIH funding to ensure compliance by the institution with the provisions of the NIH Guidelines.<sup>154</sup>The NIH Guidelines defined “recombinant DNA” as “molecules that consist of different segments of DNA which have been joined together in cell-free systems, and which have the capacity to infect and replicate in some host cell, either autonomously or as an integrated part of the host’s genome.”<sup>155</sup> The NIH Guidelines defined four

<sup>152</sup>Fredrickson, *supra*, note 128, at 27,903.

<sup>153</sup>*Recombinant DNA Research Guidelines*, 41 Fed. Reg. 27,902 (1976).

<sup>154</sup>*Id.* See Fogleman, *supra*, note 125, at 208; See also 41 Fed. Reg. 27,911 (1976).

<sup>155</sup>41 Fed. Reg. at 27,911 (1976).

levels of physical containment, designated “P1” through “P4”, whose application varied with the hazard posed by the type of research.<sup>156</sup>P1, or “minimal”, physical containment was suitable only for a laboratory that was “commonly used for microorganisms of no or minimal biohazard”, and P1 physical controls involved only “standard microbiological practices”.<sup>157</sup>Laboratories conducting “experiments involving microorganisms of low biohazard” were required to implement P2, or “low”, physical containment protocols, which included closed laboratory spaces, restricted access, daily decontamination of work surfaces, access to autoclave sterilization equipment, and use of laboratory gowns, coats, and uniforms.<sup>158</sup>Experiments of “medium” biohazard were required to implement P3 physical containment, which required most P2 controls and controlled entry, directional airflow, no work involving genetic hosts in open vessels on the open bench, posting of biohazard warning signs, decontamination of work areas after every experiment, and mandatory use of gloves.<sup>159</sup>P4, or “high”, physical containment was required for work with “microorganisms that are extremely hazardous to man and may cause serious epidemic disease”; P4 required most P3 controls and monolithic walls, sealed ducts and conduits, entry by air locks, contiguous clothing change and shower rooms, double-door autoclave steriliza-

<sup>156</sup>41 Fed. Reg. at 27,912 (1976). These four physical containment levels were based upon recommendations contained in the 1975 Statement, *supra*, note 127, which adopted the four levels defined in *Classification of Etiologic Agents on the Basis of Hazard* (4<sup>th</sup> Edition, July 1974), U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Office of Biosafety, Atlanta, Georgia, 30333.

<sup>157</sup>*Id.*

<sup>158</sup>41 Fed. Reg. at 27,913 (1976).

<sup>159</sup>*Id.*

tion equipment, maintenance of negative air pressure, exhaust treatment systems, and no removal of materials without sterilization.<sup>160</sup> In addition to separating experiments into categories of physical containment requirements, the NIH guidelines divided research protocols into specified experimental guidelines, based upon the genetic host (referred to in biology as a “vector”) and the source of the inserted DNA.<sup>161</sup> First, the experimental guidelines listed a set of six categories of experiments that were never to be performed; these experiments included the cloning of recombinant DNA from certain pathogenic organisms and oncogenic viruses, deliberate formation of recombinant genes for the biosynthesis of potent toxins, deliberate creation of plant pathogens with increased virulence or host range, deliberate transfer of drug resistance to microorganisms, certain large-scale experiments, and the deliberate release into the environment of any organism containing a recombinant DNA molecule.<sup>162</sup> The NIH Guidelines defined the relevant research vector categories as *E. Coli* K-12 vectors, purified cellular DNA vectors, plasmid, bacteriophage, and viral vectors, prokaryotic host vectors, and eukaryotic host vectors (which include subclasses of animal vectors, plant vectors, and fungal and other lower eukaryotic vectors).<sup>163</sup> The NIH Guidelines defined the relevant categories of sources of recombinant DNA as randomized shotgun clones, characterized shotgun clones, eukaryotic recombinants, prokaryotic recombinants, animal viruses, plant viruses, and eukaryotic

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<sup>160</sup>*Id.*

<sup>161</sup>See 41 Fed. Reg. at 27,914 (1976).

<sup>162</sup>41 Fed. Reg. at 27,914-5 (1976).

<sup>163</sup>41 Fed. Reg. at 27-914-20 (1976).



and prokaryotic organelle recombinants.

Two years later, NIH revised the NIH Guidelines.<sup>164</sup> The revised NIH Guidelines possessed a slightly altered definition of “recombinant DNA”.<sup>165</sup> The categories of prohibited experiments were maintained, including the prohibition on the deliberate release into the environment of any organism containing a recombinant DNA molecule, however, the revision added a process whereby specific experiments could be exempted from the prohibition on a case-by-case basis if expressly approved by the Director of NIH and by RAC after notice and opportunity for public comment.<sup>166</sup> The revised NIH Guidelines also retained the system of classification of physical containment procedure levels (P1-P4) and biological containment classifications, however, the revisions relaxed some of the requirements of these categories and expanded the class of exempt experimental protocols, in recognition of a greater familiarity with the hazards posed by certain recombinant DNA techniques.<sup>167</sup> In particular, the revised NIH Guidelines identified five categories of recombinant DNA that would be exempt from the requirements of the NIH Guidelines, concluding that these experiments “present

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<sup>164</sup>*Recombinant DNA Research, Revised Guidelines*, 43 Fed. Reg. 60,080 (1978), proposed in 43 Fed. Reg. 33,042 (1978). The revised NIH Guidelines state the reason for the 1978 revision as: “Since the issuance of the 1976 guidelines, recombinant DNA techniques have become much more widely used in research and more has been learned about the limits of potential risks in using this technology. In light of this new knowledge, the Director, NIH, on July 28, 1978 proposed substantial modification and relaxation of the guidelines.”

<sup>165</sup>43 Fed. Reg. at 60,108 (1978): “In the context of these Guidelines, recombinant DNA molecules are defined as either (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) DNA molecules that result from the replication of those described in (i) above.”

<sup>166</sup>43 Fed. Reg. at 60,108 (prohibitions), at 60,127 (case-by-case exemptions) (1978).

<sup>167</sup>See Diane E. Hoffmann, *The Biotechnology Revolution and Its Regulatory Evolution*, 38 *DRAKE L. REV.* 471 (1988/1989).

no known health risk”;<sup>168</sup> the five exempted categories included recombinant DNA that was not contained in an organism or virus, that was derived solely from a single non-chromosomal or viral DNA source, that was derived from and propagated only in a single host organism, certain DNA segments (listed in an appendix to the NIH Guidelines and periodically updated by RAC) from multiple species that exchanged DNA by known physiological processes, and any other class of DNA segments found by the Director of the NIH, after RAC review and public comment, to “not present a significant risk to health or the environment). This expanded exemption was especially significant in that these five categories of experiments together accounted for approximately one-third of the research that had been covered by the 1976 version of the NIH Guidelines.<sup>169</sup>

Although the NIH Recombinant DNA Research Guidelines did set out an initial system for the regulation of biotechnological research, the NIH Guidelines were widely criticized as inadequate. First, the NIH Guidelines were only binding upon institutions that conducted recombinant genetic research under the auspices of an NIH grant, and institutions that did not receive funding from NIH were not bound by the restrictions in the NIH Guidelines.<sup>170</sup> Many corporations voluntarily agreed to adhere to the majority of the NIH Guidelines, however, most of these corporations refused to adhere to the prohibitions on large-scale

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<sup>168</sup>43 Fed. Reg. at 60,080 (1976).

<sup>169</sup>*Id.*

<sup>170</sup>43 Fed. Reg. at 60,123 (1976) (“The Guidelines are applicable to all recombinant DNA research. . . conducted at or sponsored by an Institution that receives any support for recombinant DNA research from NIH.”).

research involving recombinant organisms.<sup>171</sup>To address these refusals, in 1980, NIH issued the Physical Containment Recommendations for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules, which, though not binding, was meant to provide guidance for large-scale recombinant DNA experiments by private institutions.<sup>172</sup>Additionally, a few local governments from areas containing large research institutions adopted legislation mandating compliance with the NIH Guidelines for all research involving recombinant genetics.<sup>173</sup>Second, even when the NIH Guidelines did apply to an institution, the only sanction that NIH could impose for violations under the NIH Guidelines was to withdraw NIH funding for research at the institution.<sup>174</sup> In an effort to bolster the enforcement powers of NIH under the NIH Guidelines, most other federal funding agencies agreed to require compliance with the NIH Guidelines by their recipient institutions as a condition precedent for continued funding.<sup>175</sup> Third, the NIH Guidelines did not apply to research utilizing genetic techniques other than recombinant DNA protocols or to genetically-modified organisms created by those techniques.<sup>176</sup>Finally, the NIH Guidelines did not set out an adequate

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<sup>171</sup> See Thomas O. McGarity & Karl O. Bayer, *Federal Regulation of Emerging Genetic Technologies*, 36 VAND. L. REV. 461 (April 1983), citing *Hearings on Science Policy Implications of DNA Recombinant Molecule Research Before the Subcommittee on Science, Research and Technology of the House Committee on Science and Technology*, 95th Cong., 1st Sess. 91,374 (1977) (testimony of Dr. Ronald E. Cape, president, Cetus Corporation and testimony of John G. Adams, vice president for scientific and professional relations, Pharmaceutical Manufacturers Association).

<sup>172</sup> *Physical Containment Recommendations for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules*, 45 Fed. Reg. 24,968 (1980).

<sup>173</sup> See 43 Fed. Reg. at 60,123 (1976).

<sup>174</sup> See Fogleman, *supra*, note 125, at 207.

<sup>175</sup> McGarity & Bayer, *supra*, note 149, at note 137, citing *Hearings Before the Subcommittee on Health and the Environment of the House Committee on Interstate and Foreign Commerce*, 95th Cong., 1st Sess. 320, 327 (1977) (testimony of Dr. Donald B. Fredrickson, Director, NIH).

<sup>176</sup> See note 126, *supra*.

system for regulating the controlled release of recombinant organisms.

In 1979, NIH was directed to prepare an NIH Risk Assessment Plan detailing the current consensus regarding known risks and hazards for all research in biotechnology.<sup>177</sup> To accomplish this task, NIH instituted the Program to Assess the Risks of Recombinant DNA Research, which was to issue annual reports of its findings.<sup>178</sup> These risk assessments concluded that there was an extremely low probability that recombinant organisms would infect humans.<sup>179</sup> The NIH, therefore, considered both making compliance with the NIH Guidelines voluntary and eliminating the NIH Guidelines entirely.<sup>180</sup> These proposals were met with strong public disfavor and were withdrawn by NIH in favor of more lenient, yet binding, NIH Guidelines, which removed deliberate release experiments from the category of prohibited research.<sup>181</sup> Beginning in 1980 and continuing for several years, the NIH Guidelines were revised on an almost annual basis, in order to reflect changes in the status of knowledge regarding the risks posed by biotechnology.<sup>182</sup> While these revisions kept the NIH Guidelines current with respect to advances in biotechnology, they did not resolve any of the above-described

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<sup>177</sup>Fed. Reg. on Sept. 13, 1979.

<sup>178</sup>*Id.*

<sup>179</sup>*National Institutes of Health, Program to Assess the Risks of Recombinant DNA Research: Proposed First Annual Update*, 45 Fed. Reg. 61,874 (1980). See McGarity & Bayer, *supra*, note 150, at 464.

<sup>180</sup>See *Recombinant DNA Research: Proposed Revised Guidelines*, 46 Fed.Reg. 59,368 (1981). See Hoffmann, *supra*, note 146, at 489. See also McGarity & Bayer, *supra*, note 150, at 465, citing *NIH Unit Votes to Ease but Retain Federal Rules on Gene-Splicing*, Wash. Post, February 9, 1982, at A7, col. 4.

<sup>181</sup>*Id.*

<sup>182</sup>The most significant of these revisions were 46 Fed. Reg. 59,368 (1981); 49 Fed.Reg. 46,266 (1984); 51 Fed. Reg. 16,958 (1986).

criticisms regarding the architecture of NIH regulation of biotechnology, and the end result of these constant modifications was to make the NIH Guidelines, in the words of the Director of NIH, “long, cumbersome, and detailed.”<sup>183</sup> Although many agreed that that the NIH Guidelines were over-detailed, it would be the lack of adequate detail regarding direct release experiments that would ultimately shift the focus of the regulation of biotechnology away from the NIH Guidelines.

During this period, FDA did not announce any official new policies regarding its regulation of products resulting from biotechnology. FDA initially embraced the NIH Guidelines and proposed their incorporation into the requirements for the design and conduct of clinical trials for products derived from biotechnology.<sup>184</sup> However, amidst the criticisms of the NIH Guidelines and the tendency of NIH to greatly relax the requirements contained therein with each revision, FDA quickly retreated from this initial position.<sup>185</sup> Instead, FDA implicitly began to adopt the position that no new product categories or significant administrative changes were need to regulate the products of biotechnology, but, that all products derived from biotechnology must undergo the entire applicable FDA review process anew regardless of whether prior manufacturers had received approval of applications covering the non-biotechnological equivalents of the products.<sup>186</sup>

<sup>183</sup>Fogleman, *supra*, note 126, at 209, citing *Evaluation of the Risks Associated with Recombinant DNA Research*, 46 Fed. Reg. 59,385, 59,391 (1981).

<sup>184</sup>43 Fed. Reg. 60,134 (1978).

<sup>185</sup>See McGarity & Bayer, *supra*, note 150, at 519-20.

<sup>186</sup>See *Id.* at 519, citing Miller, *Proceedings of the Banbury Conference on the Medical Application of Recombinant DNA* (1983).

#### IV. The Coordinated Framework for the Regulation of Biotechnology (1984 - 1986)

In the early 1980s, several incidents involving government regulation and approval of biotechnology created intense public concern regarding the safety of the products of biotechnology, the potential moral and economic impacts of seemingly-unchecked advances in biotechnology, and the ability of the existing government framework to adequately regulate advances in biotechnology.

First, in 1980, the Supreme Court held, in a controversial 5-4 decision, that a modified *Pseudomonas* bacterium possessing the genetically-engineered capability to break down multiple components of crude oil, designed for use in managing oil spills, was patentable subject matter.<sup>187</sup> This decision raised intense religious and ethical objections to the ownership of life and created a public sense of unease regarding the direction and implications of biotechnological research.

In 1982, FDA approved the first biotechnology drug, recombinant human insulin.<sup>188</sup> Human insulin is a protein involved in the regulation of sugar metabolism, and a person producing insufficient levels of insulin is afflicted with the disease diabetes.<sup>189</sup> FDA approved the NDA for recombinant insulin in record time, the

<sup>187</sup> *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). See also Senator Al Gore (United States Senator, D-Tennessee), *Planning a New Biotechnology Policy*, 5 Harv. J.L. & Tech. 19, 21 (1991).

<sup>188</sup> See Ann Gibbons, *Biotech pipeline: bottleneck ahead; a vast array of new genetically engineered drugs are heading for market - but an FDA backlog is holding them up*, SCIENCE Vol. 254, No. 5,030, pg. 369 (October 18, 1991) (available online as 1991 WL 4850080).

<sup>189</sup> See *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed.Cir.(Ind.), Jul 22, 1997).

period from NDA submission to approval taking only five months.<sup>190</sup> Prior to the advent of biotechnology, diabetes was treated by injecting patients with purified animal insulin, which, because it was not identical to human insulin, often caused allergic reactions in patients.<sup>191</sup> Recombinant human insulin, by contrast, could be constructed to be exactly identical to human insulin, and thereby eliminate these allergic reactions.<sup>192</sup> Then, in 1983, NIH and EPA together first approved several requests for authorization to conduct experiments involving the direct release into the environment of genetically-modified organisms. The first of these approvals was granted to Agracetus to conduct tests of a genetically-modified tobacco plant, discussed in detail later in this paper.<sup>193</sup> Shortly thereafter, NIH approved the environmental release of two recombinant bacteria developed by researchers at the University of California at Berkeley and Advanced Genetic Sciences, Inc. (AGS). These researchers found that two strains of naturally-occurring bacteria, *Pseudomonas syringae* and *Erwinia herbicola*, commonly found on strawberry and potato plants, produced surface proteins that encouraged the formation of ice particles and that, in the absence of these bacteria, strawberry and potato plants could survive at temperatures as low as twenty-five degrees Fahrenheit, whereas such plants in the presence of these bacteria died of frost damage at thirty-two degrees.<sup>194</sup> These re-

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<sup>190</sup>Gibbons, *supra*, note 182.

<sup>191</sup>*Id.*

<sup>192</sup>*Id.*

<sup>193</sup>This approval is discussed in detail *infra*.

<sup>194</sup>William A. Anderson, II, *Biotechnology and the Environment: The Regulation of Genetically Engineered Organisms Used in the Environment, Current Litigation Issues Associated*

searchers created deletion, or “knock-out”, recombinant strains of each of these bacteria that did not produce this frost-inducing surface protein, in the hopes that crops could be sprayed with recombinant “Ice-Minus” bacteria in order to protect the crops against frost formation.<sup>195</sup> AGS submitted a request to RAC and EPA for authorization to conduct direct release experiments under the NIH Guidelines, and NIH and EPA approved the application, scheduling the direct release experiment to begin in May of 1984. In September of 1983, prior to the planned start of these direct release experiments, however, the NIH approval was challenged in court on the grounds that NIH had violated the National Environmental Protection Act of 1969 (NEPA), because NIH had failed to prepare an Environmental Impact Statement (EIS) assessing the environmental impact of the revisions in the NIH Guidelines that removed direct releases of recombinant organisms from the “prohibited” category of experiments prior to authorization of the “ice-minus” experiment.<sup>196</sup> The District Court, in *May of with Biotechnology*, 19 Env'tl. L. Rep. 10503, 10,504 (1989); Charles Weiner, *Is Self-Regulation Enough Today?: Evaluating the Recombinant DNA Controversy*, 9 Health Matrix 289, 299 (1999).

<sup>195</sup> *Id.*

<sup>196</sup> *Foundation on Economic Trends v. Heckler*, 756 F.2d 143, 153 (D.C. Cir. 1985). National Environmental Policy Act of 1982, 42 U.S.C. § 4321 *et seq.* (1982). NEPA requires NIH to compile an environmental impact report, called an Environmental Impact Statement (EIS), prior to the approval of all major [NIH] actions significantly affecting the quality of the human environment, in order to assess the impact of such actions on the environment. This EIS report must include a “detailed statement” which discusses:

- “(i) the environmental impact of the proposed action,
- (ii) any adverse environmental effects which cannot be avoided should the proposal be implemented,
- (iii) alternatives to the proposed action,
- (iv) the relationship between local short-term uses of man’s environment and the maintenance and enhancement of long-term productivity, and
- (v) any irreversible and irretrievable commitments of resources which would be involved in the proposed action should it be implemented.”

42 U.S.C. § 4332(2)(C). See *Foundation on Economic Trends v. Heckler*, 587 F.Supp. 753 (D.D.C., May 16, 1984), at 756. See also Allen, *supra*, note 164, at 547.



1984, less than ten days prior to the scheduled start date of the “Ice-Minus” field tests, held that NIH had violated NEPA by not compiling an EIS report, and the court enjoined all direct release experiments approved by NIH, which included both the “Ice-Minus” and Agracetus tobacco experiments.<sup>197</sup> On appeal of the District Court ruling against NIH and AGS, the Court of Appeals affirmed the injunction barring the “Ice-Minus” experiment, however, the court vacated the District Court’s injunction prohibiting NIH from continuing to approve other direct release experiments, which allowed NIH to continue approval of direct release applications on a case-by-case basis.<sup>198</sup> These incidents served to create some public discomfort regarding the rapid advancement of biotechnology. In addition, NIH, in reliance on its risk assessment data, had continued to relax the regulatory requirements governing biotechnology under the NIH Guidelines throughout the early part of the 1980s. Companies conducting research in biotechnology began to complain about the inexperience of the various administrative agencies with biology and the patchwork maze of regulation that resulted. In 1984, these diverging viewpoints on the proper strength and framework for the regulations governing biotechnology aroused the attention of Congress and the President, and, in the words of then Senator Albert Gore, NIH “virtually relaxed itself out of a job.”<sup>199</sup> In 1984, the President’s Council on Natural Resources and the Environment (now the Domestic Policy

<sup>197</sup> *Foundation on Economic Trends v. Heckler*, 587 F.Supp. 753 (D.D.C., May 16, 1984).

<sup>198</sup> Anderson II, *supra*, note 168, at 10,504. See also Linda Maher, *The Environment and the Domestic Regulatory Framework for Biotechnology*, 8 J. Env’tl. L. & Litig. 133, 143 (1993).

<sup>199</sup> Gore, *supra*, note 161, at 19.

Council) established the Domestic Policy Council Working Group on Biotechnology, commonly referred to as the Working Group, under the Office of Science and Technology Policy (OSTP), to develop a coordinated system for regulating biotechnology. <sup>200</sup>The Working Group was charged with the responsibility to “insure that the regulatory process adequately considers health and environmental safety consequences of the products and processes of the new biotechnology as they move from the research laboratory to the marketplace.”<sup>201</sup>On the last day of 1984, the Working Group published the Proposal for a Coordinated Framework for Regulation of Biotechnology (the “Proposal”).<sup>202</sup>The Working Group concluded that the existing statutes and administrative agencies would be adequate to regulate biotechnology if they were properly coordinated under a single regulatory framework.<sup>203</sup>The proposed framework would interrelate the regulations of FDA, EPA, USDA, NIH, the National Science Foundation (NSF), and the Occupational Safety and Health Administration (OSHA), depending upon the type of genetic research being reviewed, and was to consist of a two-tiered system of oversight containing an interagency Coordinating Committee for Biotechnology which would oversee individual agency-based science advisory boards.<sup>204</sup>The role of the Coordinating Committee would be to “fos-

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<sup>200</sup>Hoffmann, *supra*, note 146, at 518.

<sup>201</sup>*Office of Science and Technology Policy, Proposal for a Coordinated Framework for Regulation of Biotechnology*, 49 Fed. Reg. 50,856, 50,856 (1984)

<sup>202</sup>*Id.*

<sup>203</sup>49 Fed. Reg. at 50,858. *See also* Gore, *supra*, note 161, at 23; Hoffmann, *supra*, note 146, at 518.

<sup>204</sup>49 Fed. Reg. at 50,858. *See* Marc Miller & Gregory Aplet, *Biological Control: A Little Knowledge is a Dangerous Thing*, 45 Rutgers L. Rev. 285, 324 (1993). *See also* Hoffmann, *supra*, note 146, at 518.

ter timely and coordinated decision making via interagency communication on matters of regulation; discuss matters of jurisdiction among agencies; serve as a mechanism by which agencies can raise public and concerns; and consider generic approaches for translating risk industry assessment information into policy decisions. . . [as well as] monitor the changing scene of biotechnology, and serve as a means of identifying potential gaps in regulation in a timely fashion, making appropriate recommendations for either administrative or legislative action.”<sup>205</sup>The Working Group also prepared a detailed matrix that outlined all laws, regulations and guidelines that the Working Group felt applicable to biotechnology products regarding licensing, marketing and post-marketing, export, research, patents, and emissions, as well a listing of such requirements for the various federal agencies themselves.<sup>206</sup>In addition, the Proposal contained proposed administrative policy statements, prepared by FDA, EPA, and USDA, that described the individual intra-agency regulatory frameworks within which each administrative agency would regulate the aspects of biotechnology. The FDA proposed policy statement, the FDA Statement of Policy for Regulating Biotechnology Products, began by asserting that FDA possessed “extensive experience with the administrative and regulatory regimens described as applied to the products of biotechnological processes, new and old.”<sup>207</sup>In that policy statement, FDA announced its intention to continue to regulate the products of

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<sup>205</sup>49 Fed. Reg. at 50,858.

<sup>206</sup>49 Fed. Reg. at 50,857.

<sup>207</sup>*FDA Statement of Policy for Regulating Biotechnology Products*, 49 Fed. Reg. 50,878, 50,878 (1984).

biotechnology on a case-by-case basis under its traditional regulatory scheme, looking to the “intended-use” of individual products of biotechnology in determining into which regulatory category or categories—foods, drugs, devices, or biologics—a product would be classified.<sup>208</sup>The policy statement then described the regulatory requirements applicable to each product category.

The Coordinated Framework for the Regulation of Biotechnology was first issued in draft form to allow for a public comment period, and the Working Group planned to issue final draft documents early in 1986. During the comment period, the Proposal and its statements of policy were meant to serve as interim guidelines for the regulation of biotechnology. However, these interim guidelines rapidly encountered significant difficulties in their ability to adequately control the first direct release experiments—which had in part inspired the creation of the interim guidelines themselves.

As discussed briefly above, in 1983, Agracetus, an agricultural producer, applied to RAC for approval to conduct controlled release experiments involving a genetically-modified tobacco plant.<sup>209</sup>NIH approved this direct release, however the approval was judicially enjoined by the “Ice-Minus” litigation.<sup>210</sup>To circumvent this judicially-created delay, Agracetus then submitted its application to

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<sup>208</sup>*Id.*

<sup>209</sup>*Hearings Before the Subcommittee on Natural Resources, Agriculture Research and Environment and the Subcommittee on Science, Research and Technology of the House Committee on Science and Technology*, 99th Cong., 2d Sess. 112, June 4, 5, No. 150, pg. 112-3 (1986) (testimony of Hon. Harold Volkmer) (hereinafter the “Volkmer Statement”). See also William Allen, *The Current Federal Regulatory Framework for Release of Genetically-Altered Organisms into the Environment*, 42 Fla. L. Rev. 531, 547 (1990); Hoffmann, *supra*, note 146, at 490.

<sup>210</sup>*See infra.*

USDA instead. The application was routed by USDA internally to its Animal Plant Health Inspection Service (APHIS), which decided that the genetically-modified tobacco plant was not a “plant pest” as defined under the Federal Plant Pest Act, therefore no impediment to USDA approval of the Agracetus application existed. Agracetus then used this USDA approval (or perhaps, more correctly, USDA non-action) to convince NIH to re-approve the direct release experiments in 1985. Agracetus then conducted its field tests in 1986. Shortly after Agracetus re-applied to NIH, a second corporation, Calgene, applied to USDA directly, without prior application to NIH, for approval of a direct release experiment involving a highly-similar genetically-modified tobacco plant; USDA, instead of routing the Calgene application to APHIS or to NIH, assigned review of the application to its Agricultural Recombinant DNA Research Committee (ARRC). This differing treatment of two similar applications highlighted both the inter-agency and intra-agency inconsistencies that had evolved under the NIH Guidelines system and demonstrated a stark lack of administrative coordination under the interim framework.

Several months later, an even more serious controversy arose surrounding the NIH approval of the direct release experiments involving “Ice-Minus” recombinant bacteria, discussed in detail above.<sup>211</sup> While this approval had been controversial almost from the outset, the full impact of the “Ice-Minus” incident was not felt until early 1986, when information became public that AGS, in order to obtain supporting data for its application to EPA, had conducted

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<sup>211</sup> See *infra*.

unauthorized direct release experiments of “Ice-Minus” on unenclosed trees located on the rooftop of its corporate offices in Oakland, California.<sup>212</sup> These tests were conducted by AGS as part of its application to EPA in order to determine whether “Ice-Minus” was pathogenic to fruit trees, however, the EPA application stated that the pathogenicity experiments would be conducted under controlled conditions.<sup>213</sup> When challenged by EPA, AGS asserted that a tree was a “contained facility” as that term was defined by EPA, and therefore AGS did not need EPA approval to conduct the test.<sup>214</sup> Shortly thereafter, a senate subcommittee hearing discovered that one of the “remote test sites” proposed by AGS for the “Ice-Minus” field test was in fact merely the backyard of an AGS employee, which was located in a residential neighborhood in Monterey County, California.<sup>215</sup> EPA, in its review of the AGS application, had failed to confirm the location of the test sites, and neither EPA nor AGS had disclosed the planned experiments to the Board of Supervisors of Monterey County.<sup>216</sup> When these facts became publicized, the Board of Supervisors of Monterey County passed zoning ordinances banning the “Ice-Minus” experiment.<sup>217</sup>

One month after this hearing, a third direct release violation was discovered. Techamerica Group, Inc., the inventor of a recombinant vaccine for inoculation

<sup>212</sup>Volkmer Statement, *supra*, note 166, at 114.

<sup>213</sup>*Id.*

<sup>214</sup>*Id.* See also Allen, note 166, at 548.

<sup>215</sup>*Id.*

<sup>216</sup>*Id.*

<sup>217</sup>*Id.*

against pseudo-rabies in pigs had applied to USDA for approval of direct release experiments to test the efficacy of this vaccine.<sup>218</sup>USDA approved the request without routing the application to ARRC or to NIH, and USDA did not perform an environmental assessment as required under NEPA.<sup>219</sup>The inventor then violated the NIH Guidelines by field testing the vaccine in 1,400 total pigs in multiple states without notifying or receiving the approval of the institution's IBC.<sup>220</sup>Additionally, testimony before a senate subcommittee indicated that USDA had failed to classify the vaccine as a "recombinant organism" until a significant portion of the field studies had already been conducted; even after this reclassification, the application was not submitted to ARRC or NIH.<sup>221</sup>As with the defense set forth by AGS, when Techamerica Group was challenged by USDA, it claimed that USDA approval was not required, alleging that the testing of a vaccine on pigs did not constitute an "environmental release" and that the vaccine did not constitute a "recombinant organism" because it contained no foreign DNA.<sup>222</sup>

These controversies cast grave doubts upon the claims of the drafters of the proposed coordinated framework that the existing administrative framework could adequately regulate biotechnology. The finalized version of the Coordinated Framework for Regulation of Biotechnology was originally scheduled for

<sup>218</sup>Volkmer Statement, *supra*, note 166, at 115. *See also* Allen, note 166, at 549.

<sup>219</sup>*Id.*

<sup>220</sup>*Id.*

<sup>221</sup>*Id.*

<sup>222</sup>*Id.*

publication in January of 1986, but was not issued until late June, and the controversies plaguing the interim proposed framework had a significant and visible impact upon the overall structure of the finalized framework.<sup>223</sup> The finalized version of the Coordinated Framework defined as its overall structural goal the ability to “provid[e] the opportunity for similar products to be treated similarly by particular regulatory agencies.”<sup>224</sup> To achieve this level of coordination, however, the framework relied upon careful disassociation of the agencies, rather than piecemeal harmonization, stating: “to the extent possible, responsibility for a product use will lie with a single agency”, and, “where regulatory oversight or review for a particular product is to be performed by more than one agency, the policy establishes a lead agency, and consolidated or coordinated reviews.”<sup>225</sup> The framework then set forth a detailed jurisdictional division of the regulation of the products of biotechnology between the administrative agencies.<sup>226</sup> This division relied in large part upon the basic product categories that had existed at that time as defined by FDA, USDA, and EPA.<sup>227</sup> To balance this

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<sup>223</sup>51 Fed.Reg. 23,302 (June 26, 1986). See Volkmer Statement, *supra*, note 166, at 116.

<sup>224</sup>51 Fed.Reg. at 23,302. The Coordinated Framework further stated its “two basic principles” as “(1) Agencies should seek to adopt consistent definitions of those genetically engineered organisms subject to review to the extent permitted by their respective statutory authorities; and, (2) agencies should utilize scientific reviews of comparable rigor” (*Id.* at 23,303).

<sup>225</sup>*Id.* at 23,303.

<sup>226</sup>The Coordinated Framework summarized this division of jurisdiction as follows: “Foods, food additives, human drugs, biologics and devices, and animal drug are reviewed or licensed by the FDA. Food products prepared from domestic livestock and poultry are under the jurisdiction of the USDA’s Food Safety Inspection Service (FSIS). Animal biologics are reviewed by the Animal and Plant Health Inspection Service, (APHIS). APHIS also reviews plants, seeds, animal biologics, plant pests, animal pathogens and ‘regulated articles’, i.e., certain genetically engineered organisms containing genetic material from a plant pest... Microbial pesticides will be reviewed by EPA, with APHIS involvement in cases where the pesticide is also a plant pest, animal pathogen, or regulated article requiring a permit.” (*Id.* at 23,305).

<sup>227</sup>*Id.* at 23,304 (“The manufacture by the newer technologies of food, the development of new drugs, medical devices, biologics for humans and animals, and pesticides, will be reviewed by FDA, USDA and EPA in essentially the same manner for safety and efficacy as products obtained by other techniques. The new products that will be brought to market will generally



largely disassociated structure, the framework contemplated the involvement of two coordinating groups. First, the Domestic Policy Council Working Group on Biotechnology (the “Working Group”) was to have a continued role in the finalized framework, coordinating policy matters relating to jurisdictional disputes, commercialization of products, and international harmonization.<sup>228</sup> Second, the Biotechnology Science Coordinating Committee (the “BSCC”), originally chartered on October 30, 1985, was intended to act within the finalized framework as an expert scientific advisory committee to develop coordinated scientific policies and viewpoints and to aid in the evaluation of some applications.<sup>229</sup> While an expert science advisory panel was a highly-commendable concept, the BSCC in practice, however, was plagued with problems and controversies. In 1988, the first chairman of the BSCC was charged by the Department of Justice with violating the Ethics in Government Act by failing to disclose conflicts of interest relating to the chairman’s position as director of several corporate subsidiaries of foreign biotechnology companies, and these allegations ultimately led to the replacement of the BSCC chairman.<sup>230</sup> Also, several lawyers were appointed to the BSCC, and the meetings of the BSCC were closed to the public, both of which tainted its purported role as an impartial scientific advisory committee.<sup>231</sup> The BSCC was ultimately terminated amidst criticisms of domination fit within these agencies’ review and approval regimens.”

<sup>228</sup> Maher, *supra*, note 174, at 139.

<sup>229</sup> *Id.*

<sup>230</sup> *Id.* at 140.

<sup>231</sup> *Id.*

by medical and pharmaceutical interests.<sup>232</sup>In contrast to the prominent role of NIH in the proposed framework, the finalized version of the Coordinated Framework assigned a highly-diminished position to NIH in the overall regulation of biotechnology. In commenting on this diminished role, the Coordinated Framework stated that “[a]s research experiments have expanded out of the biomedical area to environmental applications both agricultural and nonagricultural, other agencies [besides NIH] have become involved, with shifting of responsibility for research approval” to NSF, USDA, EPA, and FDA.<sup>233</sup>Each of these administrative agencies also issued finalized versions of their policy statements as attachments to the finalized Coordinated Framework. In its finalized Statement of Policy for Regulating Biotechnology Products, FDA reiterated its long-held position that “the agency need not establish new administrative procedures to deal with generic concerns about biotechnology.”<sup>234</sup>FDA restated its policy that the products of biotechnology would be reviewed on a case-by-case basis and that full FDA review would be required for “most products manufactured using new biotechnology” regardless of whether their non-biotechnological

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<sup>232</sup>*Id.* at 141.

<sup>233</sup>*Id.* at 23,305 (“Approximately ten years ago the NIH issued the NIH guidelines describing the manner in which research with organisms derived by rDNA techniques should be conducted. Since then the guidelines have been modified many times with gradual relaxation of these requirements. . . . As research experiments have expanded out of the biomedical area to environmental applications both agricultural and nonagricultural, other agencies have become involved, with shifting of responsibility for research approval to NSF (described in the November 85 Notice), USDA’s S & E, and EPA. . . . Research on foods/food additives, human drugs, medical devices and biologics will continue to rely on the NIH guidelines, with NIH approval required for certain experiments such as human gene therapy, and FDA permission for clinic trials.”). *See also* Fogleman, *supra*, note 126, at 236.

<sup>234</sup>51 Fed.Reg. 23,309, 23,313 (June 26, 1986). *See also* Kin, *supra*, note 2, at 1580.

analogs possessed FDA approval.<sup>235</sup>

Thus, the promulgation of the finalized Coordinated Framework for the Regulation of Biotechnology served to reassert the strong, centralized role of FDA as the administrative agency with primary regulatory authority over many of the products of biotechnology, and a significant amount of the research related thereto.

## V. Reforms to FDA Regulation

The early 1980s mark a significant turning point in the regulatory history of FDA. Prior to the late 1970s, FDA lacked sufficient regulatory authority to adequately ensure the safety and efficacy of its various product categories. Nearly all changes to FDA's administrative authority prior to the 1980s increased the strength and breadth of FDA's jurisdiction over its regulated products. By the end of the 1970s, Congress had expanded the administrative authority of FDA sufficiently to allow FDA to create a stable structure of thorough pre-market review and stringent post-market enforcement of the agency's regulatory policies. At the end of this period, FDA began to implement a modern system of regulation that, though sometimes burdensome and time-consuming for prod-

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<sup>235</sup>*Id.* at 23,309 (“The agency has re-examined this issue and continues to believe that, as a general principle, new marketing applications will be required for most products manufactured using new biotechnology. . . . Because of potential differences in the products resulting from use of recombinant DNA technology, the resulting products may be new products requiring separate approval under the applicable statutory provisions. However, each case will be examined separately to determine the appropriate information to be submitted. In some instances complete new applications may not be required.”).

uct manufacturers, resulted in a significantly increased level of public safety and confidence in the consumer products regulated by FDA.

The late twentieth century, however, witnessed a dramatic increase in the level of manufacturing capacity and the extent of scientific and technical knowledge available to manufacturers. These changes served to dramatically decrease both the time necessary for innovation and, as a consequence thereof, the pace of product obsolescence. The resulting trend of ever-increasing concern by manufacturers with delays in marketing products, and the communication of these concerns to Congress, began to place enormous counter-pressure upon FDA to speed the approval process for products. As a consequence of this counter-pressure, many of the changes in FDA regulation implemented by FDA and Congress during the final two decades of the twentieth century consisted of reforms intended to speed and streamline the review process for new products. This Part V discusses these two decades of reforms in detail. Subpart A discusses reforms to FDA regulation prior to the adoption of the FDA Modernization Act of 1997. For ease of organization, Subpart A first discusses administrative reform initiatives during this period, and then discusses legislative initiatives for reform, with the Prescription Drug User Fees Act of 1992 discussed in its own separate section. Subpart B discusses the FDA Modernization Act of 1997 and the reports and Congressional proposals that led to its adoption.

#### **A. Reforms to FDA Regulation Prior to 1995.**

##### **1. Administrative Reforms**

In February of 1981, President Ronald Reagan issued Executive Order 12,291, directing all federal administrative agencies to assess their existing regulatory frameworks and to suggest potential reforms.<sup>236</sup>This Executive Order established the President’s Task Force on Regulatory Relief (the “Task Force”), chaired by then Vice President George Bush, to oversee this process. The Task Force identified the FDA drug approval process as one of the twenty federal administrative programs most in need of regulatory reform.<sup>237</sup>Richard S. Schweiker, the Secretary of the Department of Health and Human Services (HHS), the administrative agency that oversees FDA, pledged in 1981 to make substantial reforms to the FDA drug approval process, in light of the findings of the Task Force.<sup>238</sup>To implement this pledge, FDA quickly proposed two sets of administrative reforms, the first set modifying the NDA portion of the drug approval process and the second modifying the IND portion, with additional administrative reforms following shortly thereafter.

In 1982, FDA issued the first of these proposed administrative reforms, the FDA Proposed New Drug and Antibiotic Regulations (called the “NDA Rewrite”), which proposed significant reforms to the NDA process.<sup>239</sup>Some of the reforms proposed to streamline the format for NDA applications in the NDA

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<sup>236</sup>46 Fed.Reg. 13,193 (1981).

<sup>237</sup>See 47 Fed.Reg. 46,622, 46,622 (1982).

<sup>238</sup>*Id.*

<sup>239</sup>47 Fed.Reg. 46,622 (1982). FDA later issued proposed regulations to implement the NDA Rewrite in 48 Fed.Reg. 26,720 (1983).

Rewrite included allowing manufacturers to include data summaries, permitting separate technical reviewers within FDA to review individual NDA applications in parallel, authorizing the submission of clinical patient data in tables of essential data rather than requiring individual case reports for every patient, reducing the number of supplemental filings required to support the initial NDA applications, expediting hearings to contest FDA disapprovals, and permitting the acceptance of foreign data studies in support of NDAs.<sup>240</sup> Additionally, the NDA Rewrite required an initial FDA response letter to new NDA applications within 180 days, stating whether the NDA was “approved”, “approvable”, or “not approved”.<sup>241</sup> These proposed reforms were finalized in three years later.<sup>242</sup> In 1983, FDA issued the FDA Proposed New Drug, Antibiotic, and Biologic Drug Product Regulations, which proposed reforms to the IND portion of the drug approval process (the “IND Rewrite”).<sup>243</sup> The IND Rewrite significantly streamlined the IND process. These reforms included allowing manufacturers greater freedom in the design and conduct of Phase I trials, clarifying IND application formats and amendment procedures, creating a “clinical hold” procedure for halting clinical research in situations where there was an unreasonable and significant risk to human subjects in order to balance the newfound Phase I freedoms, and announcing relaxation of and exemption from much of the IND process for

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<sup>240</sup>47 Fed.Reg. at 46,623.

<sup>241</sup>47 Fed.Reg. at 46,624.

<sup>242</sup>50 Fed.Reg. 7,452 (1985).

<sup>243</sup>48 Fed.Reg. 26,720 (1983).

INDs submitted to support secondary uses of already-approved drugs.<sup>244</sup>The IND Rewrite also formally proposed guidelines for “treatment INDs”. Prior to 1983, FDA had informally allowed individual physicians to sponsor and obtain secondary INDs allowing the physicians to clinically administer to patients certain unapproved new drugs undergoing the IND process if both the new drug was intended for the treatment of an incurable or terminal disease and promising data demonstrating the clinical safety and efficacy of the new drug had been obtained in Phase I and II trials.<sup>245</sup>While the IND regulations then in effect did not actually permit such secondary “treatment IND” trials, these informal treatment IND trials allowed patients to access potentially life-saving drugs approximately two to three years earlier than otherwise possible under the standard FDA approval process.<sup>246</sup>FDA made clear in the IND Rewrite that the formalized version of the treatment IND process “would be limited to patients with serious diseases or conditions, for whom alternative therapies do not exist or cannot be used.”<sup>247</sup>Additionally, in defining the level of clinical data necessary to support a treatment IND application, the IND Rewrite stated that the process was intended “primarily for drugs that have completed

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<sup>244</sup>48 Fed.Reg. at 26,721.

<sup>245</sup>48 Fed.Reg. at 26,728. *See also* Korwek, *supra*, note 50, at 136. The IND Rewrite noted that, as of 1983, “treatment IND’s submitted by individual physicians now account for approximately 30 percent of all IND’s received by FDA in a typical year.” *Id.*

<sup>246</sup>Malinowski & O’Rourke, *supra*, note 1, at 625.

<sup>247</sup>48 Fed.Reg. at 26,721. *See also Id.* at 26,729: “FDA would only authorize use of a drug under a treatment protocol/IND if it found: (1) That the proposed use is intended for a serious disease condition in patients for whom no satisfactory approved drug or other therapy is available; (2) that the potential benefits of the drug’s use outweigh the potential risks; and (3) that there is sufficient evidence of the drug’s safety and effectiveness to justify its intended treatment use.”

Phase II testing, when sufficient evidence of safety and effectiveness has already been obtained to justify making available an investigational drug for a treatment use”;<sup>248</sup> however, the IND Rewrite granted FDA administrative discretion to allow treatment IND approval prior to the end of Phase II trials in some cases, stating that “where compelling circumstances warrant, however, FDA will consider permitting treatment use earlier in the IND process.”<sup>249</sup> While the treatment IND provisions of the IND Rewrite consisted in large part of formalizing the prior informal practices of FDA, the proposed treatment IND guidelines did relax some of the principal informal requirements that FDA had imposed upon this process. Prior to the IND Rewrite, FDA only allowed physicians—not manufacturers—to sponsor treatment IND applications; the IND Rewrite made clear that both physicians and manufacturers could request treatment IND status, although physicians were required to obtain the consent of the drug manufacturer in order to cross-reference the clinical data obtained by the manufacturer under the original IND clinical trials.<sup>250</sup> The IND Rewrite also stated that “[b]ecause toxicology, chemistry, and other technical information should already be available for FDA review in the commercial sponsor’s IND, in general little or no additional supporting information would be required for either a treatment protocol or a treatment IND.” Additionally, the IND Rewrite noted that the responsibilities of manufacturers and investigators in treatment IND

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<sup>248</sup>48 Fed.Reg. at 26,721.

<sup>249</sup>48 Fed.Reg. at 26,729.

<sup>250</sup>48 Fed.Reg. at 26,723.



trials would be generally identical to, and thus not in excess of, those requirements imposed upon other clinical trials, including IRB review, data recording, and report submission requirements.<sup>251</sup>

The proposed IND Rewrite provisions were repropounded in March of 1987 and finalized two months thereafter.<sup>252</sup> The repropounded IND Rewrite explicitly listed the AIDS epidemic as a motivation for the adoption of the IND reforms.<sup>253</sup> Additionally, the repropounded regulations allowed for the limited commercial sale of a new drug during the treatment IND period, so long as FDA did not object after a thirty day pre-notification period.<sup>254</sup> Under the NDA and IND Rewrite procedures, FDA conducted a highly-expedited review of zidovudine, the first drug (later) approved by FDA to treat AIDS. In the zidovudine approval process, the manufacturer and FDA constructed a focused and well-designed Phase II trial that produced sufficient evidence to support an extensive treatment IND application. Appreciating the great need for the availability of an AIDS treatment and possessing thorough, carefully-planned Phase II data, FDA approved zidovudine for treatment of AIDS patients without Phase III trials with the added requirement that the manufacturer agree to conduct Phase IV (post-approval) research studying the effects of zidovudine in patients at an earlier stage in the progression of the AIDS virus.<sup>255</sup> This expedited approval of zidovudine resulted in the drug reaching the market in two years, rather

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<sup>251</sup>48 Fed.Reg. at 26,730.

<sup>252</sup>Repropounded 52 Fed.Reg. 8,850 (1987).

<sup>253</sup>52 Fed.Reg. 8,850, 8,850 (1987). *See also* Korwek, *supra*, note 50, at 137.

<sup>254</sup>*Id.*

<sup>255</sup>53 Fed.Reg. at 41,517

than the six to eight years normally necessary for complete FDA review.<sup>256</sup>The Task Force endorsed the finalized treatment IND procedures, and, in 1988, then Vice President Bush, acting in his capacity as Chairman of the Task Force, asked FDA to further develop procedures to allow highly-expedited review of new products intended for the treatment of life-threatening diseases, with a special focus on biomedical treatments for AIDS.<sup>257</sup>To comply with Vice President Bush's request, that same year, FDA issued the Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended To Treat Life-Threatening and Severely Debilitating Illnesses (the "Expedited Review Regulations"), in which it proposed to build upon its success with its review of zidovudine and formalize the expedited review process that it had utilized.<sup>258</sup>The Expedited Review Regulations proposed to allow manufacturers of new drugs intended for the treatment of "life-threatening and severely debilitating diseases", at the end of Phase I clinical trials, to reach an agreement with FDA on the design of adequate Phase II trials intended to provide sufficient evidence of safety and effectiveness in order to allow NDA approval without Phase III trials. If such an approval were granted, the Expedited Review Regulations allowed FDA to condition approval of the NDA upon the manufacturer's agreement to conduct Phase IV trials to fully determine the risks and optimal use of the new drug.<sup>259</sup>The Expedited Review Regulations defined the

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<sup>256</sup>*Id.*

<sup>257</sup>53 Fed.Reg. at 41,516 (1988).

<sup>258</sup>53 Fed.Reg. 41,516 (1988). *See also* Korwek, *supra*, note 50, at 138.

<sup>259</sup>53 Fed.Reg. at 41,517.

term life-threatening as “diseases where the likelihood of death is high unless the course of the disease is interrupted (e.g., AIDS and cancer), as well as diseases or conditions with potentially fatal outcomes where the end point of clinical trial analysis is survival (e.g., increased survival in persons who have had a stroke or heart attack)”;<sup>260</sup>the Expedited Review Regulations defined the term severely-debilitating diseases as “diseases or conditions that cause major irreversible morbidity (e.g., blindness or neurological degeneration).”<sup>261</sup>The IND and NDA Rewrites and Expedited Review Regulations significantly increased the access of seriously-ill patients to clinical trial protocols involving new therapies, however, many AIDS patients still could not gain access to the expedited trials, because such trials were often fully enrolled or the excluded patients did not meet the entry criteria, were too ill to participate, or were not living in an area in which such trials were being conducted. In addition, because clinical trials are required to possess a control group that does not actually receive the new drug, seriously-ill patients were often concerned that, even though they had gained access to the accelerated clinical trials, they might receive placebo controls instead of the actual new drug under investigation. In recognition of these inherent limitations in the accelerated access procedures, in 1990, FDA issued the Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People With AIDS and HIV-Related Disease (the “Parallel Track Regulations”), in which FDA proposed specialized expanded

<sup>260</sup>53 Fed.Reg. at 41,518.

<sup>261</sup>*Id.*

treatment IND trials as a third mechanism for expediting the availability of potential new AIDS therapies.<sup>262</sup>For promising new AIDS therapies that were the subject of ongoing Phase I clinical trials, the Parallel Track Regulations proposed allowing specialized additional studies of such new AIDS therapies to be conducted in parallel to Phase I trials, however, these parallel studies could be conducted without concurrent control groups for monitoring safety and without clinical entry criteria, thus all participants in the parallel study would be assured of receiving the new drug and not a placebo control.<sup>263</sup>In the Parallel Track Regulations, FDA noted that these procedures would grant patients access to unapproved drugs “at very early stages of product development” when little safety data was available, which would expose “patients to greater uncertainty and the risk of unforeseen and serious reactions.”<sup>264</sup>Because of this greatly increased risk, FDA stated that parallel track procedures would only be made available to patients that possessed advanced symptoms of AIDS, could not participate in the controlled accelerated trials, and could not take standard treatments because they were contraindicated, could not be tolerated, or were no longer effective.<sup>265</sup>Additionally, because of these greatly increased

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<sup>262</sup>55 Fed.Reg. 20,856 (1990).

<sup>263</sup>55 Fed.Reg. at 20,856.

<sup>264</sup>55 Fed.Reg. at 20,856.

<sup>265</sup>The Parallel Track Regulations set forth the following test for patient qualification:

“The determinants of patient eligibility include all of the following:

1. The patient has clinically significant HIV-related illness or is at imminent health risk due to HIV-related immunodeficiency.
2. The patient cannot participate in the controlled clinical trials because:
  - (a) The patient does not meet the entry criteria for the controlled clinical trials, or
  - (b) The patient is too ill to participate, or
  - (c) Participation in controlled clinical trials is likely to cause undue hardship (e.g. travel time) as defined by the protocol.

risks, FDA stated that the parallel track system would initially be maintained as a “pilot process” and would only be available for therapies intended for the treatment of AIDS.<sup>266</sup>The Parallel Track Regulations imposed a significant set of safeguards to protect against and minimize the risks of the system, such as very limited product selection, informed consent for every patient, physician and patient education programs, and requirements that each manufacturer establish a Data and Safety Monitoring Board for overseeing the parallel track trial procedures.<sup>267</sup>Applications to conduct parallel track trials were to be submitted to FDA as amendments to existing IND applications. These parallel track proposals would be referred by FDA to the AIDS Research Advisory Committee (AIDS RAC) of NIH which would act as an advisor to FDA, unless the manufacturer specifically asked FDA to review the proposal itself.<sup>268</sup>The Parallel Track Regulations set forth an eight factor test against which AIDS RAC and FDA would consider parallel track proposal approvals, though FDA stated that a “decision not to allow expanded availability of an investigational drug would not imply a judgment about a drug’s ultimate safety or efficacy nor preclude additional controlled trials.”<sup>269</sup>A finalized version of the Parallel Track

(d) The controlled clinical trials are fully enrolled.

3. The patient cannot take standard treatment (i.e. a drug approved for marketing or available under a treatment IND for the same clinical condition for which the investigational drug is being studied) because it is contraindicated, cannot be tolerated, or is no longer effective.”

55 Fed.Reg. at 20,858.

<sup>266</sup>55 Fed.Reg. at 20,856.

<sup>267</sup>55 Fed.Reg. at 20,858.

<sup>268</sup>*Id.*

<sup>269</sup>*See* 55 Fed.Reg. at 20,858.

Regulations was issued in 1992.<sup>270</sup> On the same day that FDA issued its finalized Parallel Track Regulations, FDA also issued the New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (the “Surrogate Endpoint Regulations”).<sup>271</sup> The Surrogate Endpoint Regulations proposed to formalize the availability of expedited approvals of new drug applications when clinical trials produced reliable evidence of the new drug’s beneficial effect “on a surrogate endpoint that reasonably suggests clinical benefit or evidence of the drug’s effect on a clinical endpoint other than survival or irreversible morbidity”, a practice which FDA had utilized informally for many years.<sup>272</sup> The Surrogate Endpoint Regulations defined an acceptable surrogate endpoint as “a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy.”<sup>273</sup> FDA also emphasized that, in gauging the risk of drug approval based upon a particular surrogate endpoint, FDA would take into consideration both the severity of the illness being treated and the extent of the benefits of the new drug over existing treatments.<sup>274</sup> Prior to the issuance of the Surrogate

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<sup>270</sup>57 Fed.Reg. 13,250 (1992).

<sup>271</sup>57 Fed.Reg. 13,234 (1992).

<sup>272</sup>*Id.*

<sup>273</sup>57 Fed.Reg. at 13,235. FDA gave the following example of an acceptable surrogate endpoint: “For example, substantially reducing elevated blood pressure has been repeatedly shown to reduce the likelihood of stroke and renal failure. Reliance on a surrogate endpoint is therefore a matter of scientific judgment, a judgment based on the available data, but still a judgment.” *Id.* at 13,235.

<sup>274</sup>57 Fed.Reg. at 13,236. In discussing its risk-benefit calculus, FDA stated the following: “Virtually all drugs can be toxic to humans, and no drug is completely free of risk. In approving a new drug for marketing, FDA analyzes benefits and risks, and approves a drug

Endpoint Regulations, FDA had informally based several drug approvals upon the favorable effect of a new drug on a surrogate endpoint, which allowed approval and marketing of drugs far before the drugs were demonstrated to effect a patients survival or overall well-being, especially for drugs intended to treat diseases that progress over a long period of time, such as AIDS.<sup>275</sup> However, FDA noted that the use of surrogate endpoints significantly increased the risk of uncertainty and of unforeseen and serious reactions, and, as with the parallel track procedures, FDA insisted on several additional safeguards in the Surrogate Endpoint Regulations. First, FDA stated that the use of surrogate endpoints would only apply to drugs meant to “provide meaningful therapeutic benefit over existing treatment for patients with serious or life-threatening diseases.”<sup>276</sup> FDA also insisted both on formal reporting requirements and on additional special reporting requirements upon the request of FDA.<sup>277</sup> As in the Expedited Review Regulations, the Surrogate Endpoint Regulations insisted that manufacturers could only receive NDA approval based upon surrogate endpoints if the manufacturers agreed to conduct timely Phase IV research to fully assess the risks if the benefit outweighs the risks. In general, the more serious the illness and the greater the effect of the drug on that illness, the greater the acceptable risk from the drug. If products provide meaningful therapeutic benefit over existing treatment for a serious or life-threatening disease, a greater risk may also be acceptable.” *Id.* at 13,236.

<sup>275</sup>57 Fed.Reg. at 13,235.

<sup>276</sup>57 Fed.Reg. at 13,234. FDA gave the following example to illustrate the requirement of a benefit over existing treatments: “For example, if there is an approved treatment for a serious or life-threatening disease, individuals or a defined subset of patients may not respond well to that therapy or be intolerant of it. A treatment shown to be effective in those patients would be eligible for these procedures.” *Id.* at 13234.

<sup>277</sup>*Id.*

of the new drug.<sup>278</sup>FDA also required submission of all promotional labeling and other materials disseminated for drugs approved based upon surrogate endpoints, fearing that such promotional materials could obscure or de-emphasize the significant risks involved with such accelerated approvals or promote inappropriate or unsafe uses of the products.<sup>279</sup>Finally, FDA retained the right to restrict the distribution of new drugs approved based upon surrogate endpoints, including restrictions requiring distribution only to certain facilities or only to physicians with special training or conditioning such distributions upon the performance of additional medical procedures for each patient receiving the new drug.<sup>280</sup> FDA issued a finalized version of the Surrogate Endpoint Regulations later that same year.<sup>281</sup>During this period of administrative reform, FDA also significantly altered its assignment of the internal review of and advising on applications involving the products of biotechnology. First, prior to 1987, the FDA Center for Drugs and Biologics possessed primary responsibility for review of NDAs for both drugs and biologics, as well as enforcement of the post-marketing provisions of the drug and biologic regulations. In 1987, in order to allow the agency to focus additional resources upon new biologics therapies for the treatment of AIDS, FDA split the Center for Drugs and Biologics into two separate centers, the first focusing purely on the regulation of drugs, the Center for Drug Evaluation and Research (CDER), and the second focusing purely on

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<sup>278</sup>57 Fed.Reg. at 13,236.

<sup>279</sup>57 Fed.Reg. at 13,237.

<sup>280</sup>*Id.*

<sup>281</sup>57 Fed.Reg. 58,943 (1992).



the regulation of biologics and the administration of the FDA AIDS program, the Center for Biologics Evaluation and Research (CBER).<sup>282</sup>To better serve the needs of biotechnology applicants, CBER was later reorganized into separate divisions, including the Division of Cytokine Biology, the Division of Cellular and Gene Therapies, and the Division of Monoclonal Antibodies.<sup>283</sup>Second, in 1990, FDA established the FDA Office of Biotechnology, in order to “enable FDA to meet the new challenges presented by advances in the area of biotechnology.”<sup>284</sup>The Office of Biotechnology was to be responsible for advising FDA on scientific issues that would have an impact on biotechnology policy, direction, and long-term goals and was to serve as the focal point for management of FDA activities relating to biotechnology research, training, contracts, and fellowship.<sup>285</sup>The Office of Biotechnology was to act as the representative of FDA in Congressional, interagency, and public-relations matters relating to biotechnology.<sup>286</sup>In addition, the Office of Biotechnology was to provide advice to all centers of FDA concerning the latest methodology for the evaluation of the safety and efficacy of the products of biotechnology.<sup>287</sup>After its creation, FDA and the Office of Biotechnology received positive feedback from the biotechnology industry, which applauded FDA’s increased focus upon and awareness of

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<sup>282</sup>52 Fed.Reg. 38,275 (1987).

<sup>283</sup>Korwek, *supra*, note 50, at 145.

<sup>284</sup>55 Fed.Reg. 12,283 (1990).

<sup>285</sup>*Id.* See also Cuttler, *supra*, note 28, at 210.

<sup>286</sup>*Id.*

<sup>287</sup>See Cuttler, *supra*, note 28, at 210.

advances in biotechnology.<sup>288</sup>

In 1991, FDA received its first application for approval of a food derived from genetically-altered plants, a tomato (called the Flavr-Savr<sup>TM</sup> tomato) modified by Calgene, Inc. to exhibit improved ripening and shelf-life. Under its authority to regulate foods, FDA could assert jurisdiction over foods derived from genetically-modified plants by considering such foods as adulterated or mislabeled, and thereby subject to post-market seizure, or as containing unapproved new food additives, and thereby subject to pre-market approval requirements; however, the exact regulatory scheme that FDA would utilize for the regulation of genetically-modified foods was unclear at the time of the Calgene application. The following year, FDA's initial experience with this application prompted FDA to announce a highly-liberalized system of regulation for foods derived from genetically-modified plants in the FDA Statement of Policy: Foods Derived from New Plant Varieties (the "1992 Statement of Policy").<sup>289</sup> In the 1992 Statement of Policy, FDA began by reiterating its long-held position that the properties of a food itself, rather than the method of production of the food, were the determinative factors in FDA review of foods.<sup>290</sup> FDA then noted that "[a]ny genetic modification technique has the potential to alter the composition of food in a manner relevant to food safety, although, based on experience, the likelihood of a safety hazard is typically very low."<sup>291</sup> The 1992 Statement of

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<sup>288</sup> *Id.*

<sup>289</sup> 57 Fed.Reg. 22,984 (1992).

<sup>290</sup> 57 Fed.Reg. at 22,984-5 ("The method by which food is produced or developed may in some cases help to understand the safety or nutritional characteristics of the finished food. However, the key factors in reviewing safety concerns should be the characteristics of the food product, rather than the fact that the new methods are used.").

<sup>291</sup> 57 Fed.Reg. at 22,988.

Policy announced that FDA would require pre-market review, under its food-additives jurisdiction, of any genetically-modified food that possessed proteins produced by recombinant genes if such proteins either differed substantially in structure or function from the proteins generally found in foods or resulted in any substance that occurred unexpectedly or at a level that may be injurious to health.<sup>292</sup>Foods containing only recombinant proteins that are substantially similar to proteins found naturally in foods would be considered generally recognized as safe, and such foods would only be subject to the general requirements for all foods.<sup>293</sup>The 1992 Statement of Policy conditioned this relaxed regulation of “substantially similar” recombinant foods by stating that FDA will carefully review all foods that possess proteins derived from recombinant material from commonly allergenic foods, such as milk, eggs, wheat, fish, tree nuts, and legumes, and FDA would require either that manufacturers of such foods demonstrate that no allergenic substances were present in the recombinant food or that the recombinant food contained adequate labeling to alert consumers to the potential risk of allergy.<sup>294</sup>In a startling display of the speed of advances in

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<sup>292</sup>57 Fed.Reg. at 22,990.

<sup>293</sup>57 Fed.Reg. at 29,990 (“Nucleic acids [the building blocks of proteins] are present in the cells of every living organism, including every plant and animal used for food by humans or animals, and do not raise a safety concern as a component of food. In regulatory terms, such material is presumed to be GRAS. . . [and]. . . When the substance present in the food is one that is already present at generally comparable or greater levels in currently consumed foods, there is unlikely to be a safety question sufficient to call into question the presumed GRAS status of such naturally occurring substances and thus warrant formal premarket review and approval by FDA. Likewise, minor variations in molecular structure that do not affect safety would not ordinarily affect the GRAS status of the substances”). See also J. H. Maryanski, *FDA’s Policy for Foods Developed by Biotechnology*, Center for Food Safety and Applied Nutrition Handout: 1995, AMERICAN CHEMICAL SOCIETY SYMPOSIUM SERIES No. 605 (1995) (Available on-line).

<sup>294</sup>57 Fed.Reg. at 22,9991. See also Maryanski, *supra*, note 269.

biotechnology, one year after the FDA issued its policy on the regulation of products derived from genetically-modified foods, FDA was confronted with the need to announce its policy on the regulation of products derived from genetically-modified people. In 1990, a four-year old girl born with Sever Combined Immune Deficiency, a rare disorder which results in immune system failure, was cured by the introduction of new recombinant genes.<sup>295</sup> These recombinant genes continued to maintain a functional immune response four years later, when the scientists involved declared the gene therapy experiment a resounding success.<sup>296</sup> By 1993, over 100 human gene therapy procedures had been approved worldwide, and some of these manufacturers and researchers requested FDA to clarify its policies for the regulation of gene therapy trials.<sup>297</sup> To respond to this request, in 1993, FDA issued the FDA Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products (the “Gene Therapy Policy”).<sup>298</sup> In the Gene Therapy Policy, FDA divided products intended for genetic manipulation into two separate categories: “somatic cell therapy products” and “gene therapy products”.<sup>299</sup> The Gene Therapy Policy

<sup>295</sup>Ralph Oman, *Biotech Patenting Issues Raise Ethical Concerns*, Nat'l L.J., May 8, 1995, at C42. See also Malinowski & Maureen A. O'Rourke, *supra*, note 1, at 174.

<sup>296</sup>Dolores Kong, *Study: First Gene Therapy a Success*, Boston Globe, Oct. 20, 1995, at 3. See also Malinowski & O'Rourke, *supra*, note 1, at 174-5.

<sup>297</sup>Malinowski & O'Rourke, *supra*, note 1, at 175. See also 58 Fed.Reg. 53,248, 53,248 (1993). Other genetic disorders include cystic fibrosis (1 in 2,500 white births), down syndrome (1 in 1,000 births), muscular dystrophy (1 in 3,300 male births), fragile X syndrome (1 in 1,500 male births), hemophilia A (1 in 8,500 male births), Huntington's disease (1 in 25,000 births), polycystic kidney disease (1 in 3,000 births), sickle-cell anemia (1 in 600 black births), and Tay-Sachs disease (1 in 3,600 Jewish births). From Frederic Golden, *Good Eggs, Bad Eggs*, TIME, January 11, 1999.

<sup>298</sup>58 Fed.Reg. 53,248 (1993).

<sup>299</sup>*Id.*

defined “somatic cell therapy products” as “autologous (i.e., self), allogeneic (i.e., intra-species), or xenogeneic (i.e., inter-species) cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo to be administered to humans and applicable to the prevention, treatment, cure, diagnosis, or mitigation of disease or injuries.”<sup>300</sup> Because somatic cell therapy procedures involved the introduction of genetically-modified whole cells into humans, FDA maintained that such products constituted both a drug and a biologic, and, as such, would be required to complete the IND and NDA process and comply with any CGMP guidelines in addition to satisfying the ELA and PLA licensure requirements.<sup>301</sup> “Gene therapy products”, by contrast, were defined as “products containing genetic material administered to modify or manipulate the expression of genetic material or to alter the biological properties of living cells.”<sup>302</sup> FDA stated that gene therapy products contained in viral vectors constituted both a biologic and a drug, whereas such products contained in a chemically-synthesized vector system met only the definition of a drug.<sup>303</sup> In 1995, to address complaints that products of gene therapy were subject to double regulation, the NIH Guidelines were amended to create a consolidated procedure for NIH and FDA review of gene therapy trials.<sup>304</sup> Additionally, following the release of the Gene Therapy Policy,

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<sup>300</sup>58 Fed.Reg. at 53,249.

<sup>301</sup>*Id.*

<sup>302</sup>*Id.*

<sup>303</sup>*Id.*

<sup>304</sup>60 Fed.Reg. 20,726 (1995).

CBER proposed in 1994, and Congress mandated in 1995, that FDA develop a gene therapy patient data registry under FDA's Computerized Submission Management and Review Tracking System program.<sup>305</sup> Early gene therapy trials did not have the impact desired by scientists. Most early gene therapy trials failed in the Phase I portion of research, as many recombinant genes inserted into humans either did not functionally express proteins or achieved functional expression for a short time and then inexplicably ceased to function.<sup>306</sup> An early gene therapy trial for cystic fibrosis utilized an adenoviral vector that resulted in such severe inflammation that FDA ordered the termination of the clinical trial, and this failure served to greatly increase public concern over the safety of gene therapy.<sup>307</sup> Over thirty states eventually passed laws banning gene therapy and limited or prohibited the ability of health care insurers to discriminate against persons with genetic disorders.<sup>308</sup> One of the few gene therapy procedures actually reaching Phase III trials involved the treatment of brain cancer by utilizing a virus that only infects dividing cells in order to facilitate the introduction into brain cells of a recombinant gene derived from the herpes virus.<sup>309</sup> The insertion of this gene made all genetically-modified brain cells highly sensitive to a standard herpes treatment (ganciclovir), and, because only cancerous brain cells undergo cell division, the gene was selectively introduced only into cancerous

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<sup>305</sup>Noguchi, *supra*, note 47, at 370.

<sup>306</sup>Leon Jaroff, *Fixing the Genes*, TIME, January 11, 1999.

<sup>307</sup>*Id.*

<sup>308</sup>Christopher Hallowell, *Playing the Odds*, TIME, January 11, 1999.

<sup>309</sup>Jaroff, *supra*, 280.

cells, which died upon treatment with ganciclovir.<sup>310</sup>

## 2. Legislative Reforms

ORPHAN In addition to these administrative reforms for accelerating approval, beginning in DRUG ACT

OF 1983, 1983, Congress adopted two sets of legislative reforms designed to alleviate significant disincentives created by the burdens of the FDA approval process. Conducting clinical trials sufficient to support an adequate NDA was extremely expensive, and Congress and FDA quickly realized this expense created a large disincentive for manufacturers to promote drugs intended for the treatment of rare diseases. FDA initially attempted to address this disincentive by allowing many such drugs, called “orphan drugs”, to remain indefinitely covered by an approved IND while allowing the manufacturers to administer the orphan drugs to patients in quasi-clinical trials.<sup>311</sup> However, this administrative solution ultimately proved unsatisfactory, and, to remedy this situation, Congress passed the Orphan Drug Act of 1983.<sup>312</sup> The Orphan Drug Act provided that the manufacturer of a drug designated as an “orphan drug” by FDA was entitled to a fifty percent tax credit for the cost of conducting clinical trials, could request federal funding to assist in the conduct of the clinical trials, and, if FDA ultimately approves the manufacturer’s NDA application, was entitled to market exclusivity for seven years.<sup>313</sup> “Orphan drug” status could be

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<sup>310</sup>*Id.*

<sup>311</sup>Hutt & Merrill, *supra*, note 2, at 566.

<sup>312</sup>Pub. L. No. 97-414, 96 Stat. 2,049, codified as amended at 21 U.S.C. ♣♣ 360aa *et seq.* (Jan. 4, 1983). FDA published implementing guidelines in 48 Fed.Reg. 40,784 (1983).

<sup>313</sup>*See* Malinowski & O’Rourke, *supra*, note 1, at 202. *See also* Hutt & Merrill, *supra*, note

conferred by FDA on any drug that was intended primarily to treat a “rare disease or condition”.<sup>314</sup> Shortly after the adoption of the Orphan Drug Act, Congress amended the definition of “rare disease or condition” to include any disease or condition that affects less than 200,000 people.<sup>315</sup> Additionally, in the IND Rewrite, FDA identified orphan drugs as “leading candidates” for the treatment IND process.<sup>316</sup> While the Orphan Drug Act did serve its purpose and incentivise the treatment of rare diseases, the Act also resulted in a substantial amount of litigation regarding the extent of “similarity” necessary to trigger the protections of the seven year exclusivity period.<sup>317</sup>

One year after the adoption of the Orphan Drug Act, Congress again attempted to remedy two additional disincentives created by the FDA regulatory structure. Manufacturers of novel drugs and devices often obtain patent protection for their inventions, the term of which at that time lasted seventeen years from the date of issuance of the patent.<sup>318</sup> Because of the great expense involved in obtaining FDA approval, most manufacturers refused to commence clinical trials before they were assured of the availability of patent protection for their inventions, which would guarantee market exclusivity and allow the manufacturer to recoup its investment. Full FDA review of products, however, often required six or more years to reach completion.<sup>319</sup>This essentially resulted

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2, at 566.

<sup>314</sup>21 U.S.C. \_\_\_.

<sup>315</sup>Health Promotion and Disease Prevention Amendments of 1984, 98 Stat. 2815 (1984).

<sup>316</sup>48 Fed.Reg. 26,720, 26,721 (1983).

<sup>317</sup>Korwek, *supra*, note 50, at 148-9. See e.g. *Genentech v. Bowen*, 676 F.Supp. 301 (D.C.D.C. 1987), Hutt & Merrill, *supra*, note 2, at 567.

<sup>318</sup>35 U.S.C.A. ♣154.

<sup>319</sup>See Merrill, *supra*, note 17, at 1,792.



in a forfeiture by manufacturers of a significant portion of their seventeen year patent term while involved in the FDA review process. The effect of this forfeiture on manufacturers of pioneer drugs was mitigated, however, by the FDA treatment of generic (“me-too”) drugs. After the adoption of the Drug Amendments of 1962, FDA instituted the requirement that all generic drugs be the subject of their own approved NDA prior to marketing. However, FDA had long maintained the position that the clinical data submitted in the pioneer NDA application was confidential and constituted trade secrets of the pioneer manufacturer.<sup>320</sup> Because generics manufacturers could not initiate clinical trials prior to expiration of the pioneer drug patent and then could not incorporate by reference the confidential safety and efficacy data that had supported the pioneer NDA, generics manufacturers were forced either to undergo the full FDA approval process, thus extending the period of market exclusivity of the pioneer drug (this additional exclusivity is often referred to as a “second patent”), or to purchase permission from the pioneer manufacturer to utilize the pioneer clinical data in the generic drug NDA, thereby allowing the manufacturer to extract license fees and royalty payments.<sup>321</sup>

DRUG PRICE            To attempt to reverse both of these disincentives to manufacturers, Congress COMPETITION AND PATENT adopted the Drug Price Competition and Patent Term Restoration Act of 1984 (the TERM RESTORATION “1984 Act”).<sup>322</sup> The 1984 Act essentially embodied a com-

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<sup>320</sup> See Merrill, *supra*, note 17, at 1,792.

<sup>321</sup> FDA’s position that all clinical data constituted confidential information not discoverable under the Freedom of Information Act was upheld in court. *Tri-Bio Laboratories v. United States*, 836 F.2d 135 (3<sup>rd</sup> Cir. 1987); *Public Citizen Health Research Group v. FDA*, 704 F.2d 1280 (D.C. Cir. 1983). See Merrill, *supra*, note 17, at 1,793.

<sup>322</sup> Pub. L. No. 98-417, 98 Stat. 1,585 (Sept. 24, 1984) (the “1984 Act”).

promise struck between ACT OF 1984

manufacturers of pioneer and generic products. To remedy the loss of pioneer manufacturer's patent life, the 1984 Act allowed pioneer manufacturers to extend the life of their patent by adding half of the time spent in the IND process and all of the time during which an NDA application was reviewed by FDA, up to a combined maximum of fourteen years.<sup>323</sup> In compromise for this extended patent protection, the 1984 Act allowed manufacturers of generic products to rely upon the clinical data submitted to support approval of the pioneer NDA.<sup>324</sup> This compromise successfully realigned the incentives of pioneer and generic drug manufacturers.

The same sense of urgency for new treatments effective against AIDS, cancer, and other incurable diseases that had prompted Congressional and administrative actions loosening the regulation of drugs in the 1980s animated a set of reforms strengthening the regulation of medical devices. In the mid 1980s, several reports of the General Accounting Office (GAO), the Office of Technical Assessment (OTA), and the Office of Inspector General of HHS (OIG), each of which had conducted investigations of FDA regulation of devices, concluded that the authority granted to FDA under the Device Amendments of 1976 was inadequate in its ability to allow FDA to compel disclosure of device related problems by device user facilities (hospitals, nursing homes, ambulatory surgical facilities, and outpatient treatment facilities) or allow FDA to follow up

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<sup>323</sup>1984 Act § 201(c), (g), 98 Stat. 1,619, codified at 35 U.S.C. §156. *See also* Korwek, *supra*, note 50, at 137.

<sup>324</sup>1984 Act § 104, 98 Stat. 1,610.

on any such disclosures once made.<sup>325</sup> A 1986 report from a GAO study stated that more than ninety-nine percent of device-related problems occurring in hospitals were not reported to FDA.<sup>326</sup> Other reports found that many hospitals were actually unaware of their reporting obligations to FDA regarding device failures.

SAFE To remedy this under-reporting by device user facilities, in 1990, Congress MEDICAL DEVICES adopted the Safe Medical Devices Act of 1990 (the “1990 Act”).<sup>327</sup> The 1990 Act made ACT OF 1990

numerous alterations to the provisions of the 1976 Amendments.<sup>328</sup> The 1990 Act required that device user facilities, or in some cases the medical device manufacturer, report to FDA any deaths, serious illnesses, injuries, adverse effects, or deficiencies related to medical devices used by patients or employees of the facility within 10 days after such occurrence, as well as requiring that facilities file a semiannual report to FDA summarizing all such interim reports filed with FDA or manufacturers.<sup>329</sup> The 1990 Act also required manufacturers of medical devices that possessed potentially serious adverse health risks or that were either life-sustaining or permanently-implantable to develop and maintain a system for tracking and, if necessary, recalling such medical de-

<sup>325</sup>56 Fed.Reg. 60,024, 60,025 (1991). See also Theodosia Tamborlane, *The FDA Moves to Implement the Safe Medical Devices Act*, 9 NO. 10 HealthSpan 7, 7 (1992).

<sup>326</sup>*Id.*

<sup>327</sup>Pub. L. No. 101-629, 104 Stat. 4,511, codified in various provisions of 21 U.S.C. ♣ 360a *et seq.* (Nov. 28, 1990).

<sup>328</sup>See Hutt & Merrill, *supra*, note 2, at 746, 750.

<sup>329</sup>Safe Medical Devices Act ♣ 519(b)(1). See 56 Fed.Reg. at 60,025. See also Charles J. Raubicheck, *The FDA's Implementation of the Safe Medical Devices Act of 1990*, 46 Food Drug Cosm. L.J. 885, 885.

vices.<sup>330</sup>Such devices must also be the subject of a plan of post-market surveillance that is pre-approved by FDA after clearance by an FDA advisory committee.<sup>331</sup>To enforce the findings of post-market surveillance and reporting requirements, the 1990 Act granted FDA the authority to recall any device that posed a reasonable probability of causing serious adverse health consequences or death.<sup>332</sup>Additionally, the 1990 Act charged FDA with providing education and information to facilities that possessed reporting responsibilities under the 1990 Act reporting provisions.<sup>333</sup>

While these legislative changes strengthened the enforcement powers of FDA, the 1990 Act also relaxed some of the requirements of FDA approval of medical devices. The 1990 Act clarified the treatment of predicate (“piggyback”) devices by making explicit FDA’s informal practice of allowing new devices to claim substantial equivalence to a prior-approved predicate device, and thereby avoid Class III status and pre-market approval requirements, if the new device has the same intended use as the predicate device and either has the same technological characteristics or has data demonstrating that the new device is at least as safe and effective as the predicate device.<sup>334</sup> Further, the 1990 Act established a “Humanitarian Device Exemption”, similar to the Orphan Drug Act exemption, under which any device intended to treat a disease affecting less than

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<sup>330</sup>21 U.S.C. § 360i(e). Raubicheck, *supra*, note 276, at 886.

<sup>331</sup>21 U.S.C. § 360k. Raubicheck, *supra*, note 276, at 887.

<sup>332</sup>21 U.S.C. § 360h(e). Raubicheck, *supra*, note 276, at 889.

<sup>333</sup>Safe Medical Devices Act § 2(d). *See* 56 Fed.Reg. at 60,025.

<sup>334</sup>Safe Medical Device Act § 513(i). *See* Hutt & Merrill, *supra*, note 2, at 756. *See also* Raubicheck, *supra*, note 276, at 889.

four-thousand people would be exempted from PMA and Class II requirements, subject to certain commercial sale restrictions.<sup>335</sup>

### 3. The Prescription Drug User Fees Act of 1992

PRESCRIPTION Although FDA had made significant reforms to its regulations of drugs, by early DRUG USER FEES ACT in the 1990s, manufacturers and patients were still complaining that new drug review OF 1992

times were unacceptably long. FDA, in response, noted that the major impediment to faster new drug approval rates was the lack of a sufficient number of qualified staff to handle the ever-increasing number of applications. To address this impediment, Congress adopted the Prescription Drug User Fee Act of 1992 (“PDUFA”), which authorized FDA to collect user fees from drug manufacturers.<sup>336</sup> The concept of FDA user fees was not novel when proposed in 1992. GAO had recommended to Congress that FDA collect user fees for NDA application review in 1971, and the President’s Private Sector Survey on Cost Control echoed this recommendation in 1983.<sup>337</sup> Almost every year following the release of this report, the President’s budget proposal has included a recommendation for FDA user fees to substitute for budget revenues; however, FDA had steadfastly opposed such fees, and Congress supported FDA by deleting the user fees from the budget.<sup>338</sup> Congress was concerned that the assessment of uniform user fees would unfairly disadvantage small businesses and orphan drug producers, however, politically there was no alternative solution

<sup>335</sup>21 U.S.C. s 360j(m). See Raubicheck, *supra*, note 276, at 889.

<sup>336</sup>Pub. L. No. 102-335, 106 Stat. 941 (Aug. 26, 1992).

<sup>337</sup>Government Accounting Office, *Fees Not Charged for Processing Applications for New Drugs* (1971); President’s Private Sector Survey on Cost Control, *Task Force Report on User Charges* 271-74 (1983). See also Bruce N. Kuhlik, *Industry Funding of Improvements in the FDA’s New Drug approval Process: the Prescription Drug User Fee Act of 1992*, 47 FOOD & DRUG L. J. 483, 487 (1992).

<sup>338</sup>Kuhlik, *supra*, note 291, at 487.

to allocate adequate additional funding to FDA.<sup>339</sup> PDUFA represented a compromise between all of these concerns. PDUFA authorized FDA to collect user fees, in amounts increasing each year, for NDA applications and amendments, annual fees collected for each manufacturing establishment that produces prescription drugs, and annual fees collected for each prescription product approved for marketing.<sup>340</sup> These fees, however, were significantly reduced, deferred, or waived entirely for businesses employing less than five-hundred employees.<sup>341</sup> The collection of these fees allowed FDA to hire an additional 620 reviewers.<sup>342</sup> These additional reviewers, in turn, allowed FDA to create a special new class of applications that would receive preferential, and thereby expedited, review; these expedited applications were referred to as “priority” or “Type P” applications.<sup>343</sup>

In exchange for the authority to collect user fees, Congress required FDA to propose an aggressive set of improved-performance milestones for CDER and CBER. Because FDA would require a significant period of time in which to hire and train its new reviewers, these milestones were composed with increasing requirements set for each year until the full set of improvements was to be in place in 1997.<sup>344</sup> To ensure FDA compliance with these milestones, Congress only authorized PDUFA for five years, and thus the user fee authority would

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<sup>339</sup>Mary Beth Bierut, *The Prescription Drug User Fee Act of 1992: Speeding Up the Drug Approval Process*, 9 NO. 11 HEALTHSPAN 13, 15 (December 1992).

<sup>340</sup>\_\_\_\_\_. See Bierut, *supra*, note 293, at 13.

<sup>341</sup>\_\_\_\_\_. See Bierut, *supra*, note 293, at 13.

<sup>342</sup>Malinowski & O'Rourke, *supra*, note 1, at 210.

<sup>343</sup>*Id.*

<sup>344</sup>See Robert Temple, M.D., *Commentary on “The Architecture of Government Regulation of Medical Products”*, 82 Va. L. Rev. 1877, 1881 (1996).

need to be authorized again by Congress in 1997. These improvement milestones were not contained in PDUFA itself, however, but were proposed in two letters written by FDA Commissioner David A. Kessler, M.D., one month prior to the eventual adoption of PDUFA and sent to Chairman John Dingell and Ranking Minority Member Norman Lent of the House Committee on Energy and Commerce and Chairman Edward M. Kennedy and Ranking Minority Member Orrin G. Hatch of the Senate Committee on Labor and Human Resources. The goals set forth by Commissioner Kessler were ambitious: to review and act on “priority” applications and “priority” amendments within six months after submission, “standard” applications within twelve months after submission, “standard” amendments within six months after submission if no review of clinical data was required or within twelve months after submission if clinical data must have been reviewed to support approval of the amendment, and complete applications resubmitted following issuance of a non-approval letter within six months after submission.<sup>345</sup> In this context, to “act on” was “understood to mean the issuance of an action letter after the filing of an application... [that], if it is not an approval, or approvable letter, will set forth in detail the specific deficiencies and, where appropriate, the actions necessary

<sup>345</sup>Letter from David A. Kessler, M.D., Commissioner of Food and Drugs, to Rep. John D. Dingell and Rep. Norman Lent (Sept. 14, 1992); Letter from David A. Kessler, M.D., Commissioner of Food and Drugs, to Senator Edward M. Kennedy and Senator Orrin G. Hatch (Sept. 14, 1992) (hereinafter collectively the Kessler September 14 letter); Letter from David A. Kessler, M.D., Commissioner of Food and Drugs, to Rep. John D. Dingell and Rep. Norman Lent (Sept. 22, 1992); Letter from David A. Kessler, M.D., Commissioner of Food and Drugs, to Senator Edward M. Kennedy and Senator Orrin G. Hatch (Sept. 22, 1992) (hereinafter collectively the Kessler September 22 Letter). Reprints of these letters are contained in 138 Cong. Rec. H9099, H9099-9100 (daily ed. Sept. 22, 1992). For a thorough review of these letters and their impact on Congressional legislation, see Kuhlik, *supra*, note 291, at 488-491.

to place the application in condition for approval.”<sup>346</sup> Commissioner Kessler further proposed that FDA would review and act on all backlogged NDA, PLA, and ELA applications within twenty-four months after initiation of the user fee payment system.<sup>347</sup> Commissioner Kessler also set interim application goals, under which FDA would review an increasing percentage of each succeeding new year’s submitted applications and amendments within the specified milestone periods, beginning with fifty-five percent in 1994 and increasing to ninety percent in 1997.<sup>348</sup> To gain the support of non-prescription drug manufacturers for PDUFA, Commissioner Kessler’s second letter made some of these improved review times applicable to non-prescription drug applications and amendments as well.<sup>349</sup>

While FDA was in the initial stages of implementing the user fee system and improved performance goals for drugs, the House Committee on Oversight and Investigations, also Chaired by Rep. John Dingell, released a highly critical report of the FDA implementation of its device regulation program under the 1990 Act, entitled “Less Than the Sum of Its Parts”.<sup>350</sup> FDA relied upon this report to recommend an extension of the user fees program to medical device applications, however, when legislation was proposed to implement this recommendation, it faced significant industry opposition and was therefore never adopted.<sup>351</sup>

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<sup>346</sup>Kessler September 14 Letter, 138 Cong. Rec. at H9099.

<sup>347</sup>*Id.*

<sup>348</sup>*Id.*

<sup>349</sup>Kessler September 22 Letter, 138 Cong. Rec. at H9099-9100.

<sup>350</sup>H.R. REP. NO. 103-N, 103d Cong., 1st Sess. 5 (1993).

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The use of user fees in the regulation of drugs significantly decreased the time required for product approvals by FDA. Prior to the adoption of PDUFA, FDA had been criticized upon comparison to drug review in France and England, both of which approved drugs significantly faster than FDA on a consistent basis. Between 1992 and 1996, six antiviral therapies developed for the treatment of AIDS were developed, and, with the added resources supplied by user fees, FDA reviewed and approved five of these six therapies faster than either France or England, with the sixth therapy approved simultaneously by all three agencies.<sup>352</sup> In approvals outside the AIDS context, FDA consistently compared well to these foreign drug approval agencies, and FDA was the first to approve new products whose intended uses spanned a wide range of diseases, such as cancer, leukemia, cystic fibrosis, multiple sclerosis, Lou Gehrig's disease, and Alzheimer's disease.<sup>353</sup> While the adoption of PDUFA and the collection of user fees by FDA substantially decreased the time required for product approvals, FDA quickly realized that administrative reliance upon user fees became golden handcuffs, and, in 1997, when PDUFA would require reauthorization by Congress, industry representatives could exert significant leverage against FDA by lobbying Congress to tie further regulatory reforms to the reauthorization of PDUFA.

#### **B. The FDA Modernization Act of 1997**

<sup>352</sup>David A. Kessler, M.D., Commissioner, Food and Drug Administration, *Statement Before the Committee on Labor and Human Resources, United States Senate*, February 21, 1996 (available on-line [www.fda.gov](http://www.fda.gov)).

<sup>353</sup>*Id.*

In 1993, President Clinton created the National Performance Review (NPR), later renamed the National Partnership for Reinventing Government, which was headed by Vice President Gore. The stated “mission” of the NPR was to review and propose reforms to all administrative agencies in order “to create a government that works better, costs less, and gets results Americans care about.”<sup>354</sup> The NPR identified FDA as one of thirty-two “High Impact Agencies”, which were selected “based on their high degree of interaction with the public, business, or the operation of other federal agencies.”<sup>355</sup> In 1995, Vice President Gore requested the directors of each of these High Impact Agencies to propose “a small handful of significant, concrete, measurable goals that c[ould] be achieved over the next three years.”<sup>356</sup>

In response to this request, FDA proposed two separate sets of administrative reforms, many of which consisted of extensions of existing FDA reform initiatives. In April of 1995, the first set of these reforms were published in an NPR report co-authored by President Clinton and Vice President Gore entitled *Reinventing Drug & Medical Device Regulations* (“Reinventing America I”).<sup>357</sup> As discussed earlier, FDA had traditionally required that companies construct full-scale working manufacturing plants prior to receiving ELA and PLA

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<sup>354</sup>John Kamensky, *National Partnership for Reinventing Government: A Brief History*, January 1999 (available on-line at [www.npr.gov](http://www.npr.gov)).

<sup>355</sup>National Partnership for Reinventing Government, “*High Impact Agencies: A Background Paper*”, September 1998 (available on-line at [www.npr.gov](http://www.npr.gov)).

<sup>356</sup>Kaensky, *supra*, note 350.

<sup>357</sup>President Bill Clinton & Vice President Al Gore, *Report of the National Performance Review: Reinventing Drug & Medical Device Regulations*, April 1995 (“Reinventing America I”).

license approvals, thereby requiring these companies to make large up-front investments in facilities for unapproved drugs and biologicals that might never reach market. Further, FDA had also required that, once such licensing approval was granted, companies receive prior FDA approval before instituting any significant changes to licensed manufacturing facilities or processes. In the Reinventing America I report, FDA stated that it would allow companies to receive ELA and PLA approvals for pilot and small-scale manufacturing facilities and would eliminate many of the requirements for pre-approval of changes to manufacturing plants and facilities.<sup>358</sup> For biologicals not concurrently regulated as drugs, FDA proposed a three-tiered categorization of changes to biological manufacturing plants and facilities: Category I changes would include mere relocations of equipment, tightening of existing specifications, and changes in the supplier of components and would require no supplemental reports to FDA; Category II changes, including expansions of manufacturing support systems, modifications to manufacturing areas, and replacement of old equipment with equipment of similar but not identical design, would require submission of a standard reporting supplement to FDA and a thirty-day waiting period in which FDA could challenge the modifications; and Category III changes, including alterations in processing conditions, dosage forms, and dating periods, would continue to require prior approval by FDA.<sup>359</sup> Also in the Reinventing America I report, FDA, in a formalization of its practices under the Expedited Review

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<sup>358</sup>Reinventing America I, *supra*, note 354, at 4-10.

<sup>359</sup>*Id.* at 8. See also Food and Drug Administration, *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*, 62 Fed.Reg. 39,904 (July 24, 1997).

procedures, announced that in limited cases it would no longer require multiple clinical trials to support an NDA application if one adequately-designed multi-center clinical trial could be constructed, citing the zidovudine approval as an example of such practices.<sup>360</sup> To assist in the structuring of such clinical trials, FDA issued a revised statement of policy clarifying the requirements utilized by FDA in determining safety and effectiveness.<sup>361</sup>

In the Reinventing America I report, FDA further proposed several changes to medical device regulation. First, FDA announced its intention to exempt from pre-market review nearly 125 additional categories of low-risk medical devices.<sup>362</sup> FDA also finally acquiesced to the long-standing industry proposal for the creation of a pilot program for the limited external review by private FDA-accredited institutions of certain 510(k) “substantial equivalence” applications for several categories of low risk medical devices, modeled after a similar system of private-sector review utilized in the European Community.<sup>363</sup> This private institutional review of medical devices was to be supported by user fees, and FDA further reiterated its proposal from two years earlier for the authorization of medical device user fees for all FDA administrative activities.<sup>364</sup>

Seven months after the publication of the Reinventing America I report, the

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<sup>360</sup>*Id.* at 28-29. The zidovudine clinical trial is discussed *infra*.

<sup>361</sup>Food and Drug Administration, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and biological Products*, 63 Fed.Reg. 27,093 (May 15, 1998), proposed at 62 Fed.Reg. 13,650 (March 21, 1997).

<sup>362</sup>*Id.* at 5.

<sup>363</sup>*Id.* at 20. See also Pilot & Waldmann, *supra*, note 91.

<sup>364</sup>*Id.* at 20-22. Such general device user fees had been predicted to raise over \$23 million in revenues for FDA if implemented. *Id.*

second set of reforms proposed by FDA was published in a second NPR report entitled *Reinventing the Regulation of Drugs Made from Biotechnology* (“Reinventing America II”).<sup>365</sup> The goal of this second set of reforms was to harmonize the regulation by CBER (biologics) and CDER (drugs) of “well-characterized” biotechnological drug products, which both of these FDA centers had regulated on a case-by-case basis as either drugs, biologics, or both.<sup>366</sup> To this end, for such “well-characterized” biotechnology products, FDA announced that it would eliminate the requirement of separate ELA and PLA license applications for biotech manufacturing facilities, essentially formalizing its then current administrative practice of allowing relaxed inspections to support ELA approvals for facilities producing “well-characterized” biological drugs, and FDA further proposed to cease requiring individual lot samples for every batch of “well-characterized” biotechnology drug products.<sup>367</sup> The ELA application requirement was replaced by a system of more thorough post-marketing inspections by CBER to ensure CGMP compliance, and the PLA application was modified to be harmonized with a new NDA application format that incorporated some of the information formerly contained in the ELA applications.<sup>368</sup> The elimina-

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<sup>365</sup>President Bill Clinton & Vice President Al Gore, *Report of the National Performance Review: Reinventing the Regulation of Drugs Made from Biotechnology*, November 1995 (available on-line at [www.fda.gov](http://www.fda.gov)) (“Reinventing America II”).

<sup>366</sup>*Id.*

<sup>367</sup>*Id.* See Pilot & Waldmann, *supra*, note 91.

<sup>368</sup>*Id.* Implemented in *Final Rule: Elimination of the Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products*, 61 Fed.Reg. 24,227 (1996); *Interim Definition and Elimination of Lot-by-Lot Release for Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products*, 60 Fed.Reg. 63,048 (1995). See Food and Drug Administration, Department of Health and Human Services, *Vice President Al Gore Recognizes FDA’s Program to Improve Inspections*, HHS News P98-14, April 21, 1998 (available on-line at [www.fda.gov](http://www.fda.gov))

tion of the ELA requirement would also allow manufacturers of biotechnology products to contract out many of their manufacturing processes to third-parties, placing them on more equal footing with their competitors manufacturing synthetic non-biotechnological products.<sup>369</sup> These changes essentially allowed all “well-characterized” biotechnology products regulated as drugs to escape the majority of the requirements of concurrent regulation as biologics.

The Reinventing America II report also contained FDA proposals for generalized reforms applicable to all drugs and biologics. Prior to the Reinventing America II report, FDA had required manufacturers of biological products to designate a single person as a “Responsible Head” to exercise control of the manufacturing facility and ensure compliance with all applicable CGMP regulations. This requirement had proven burdensome for companies with large production facilities in multiple locations, and, to remedy this difficulty, FDA stated in the Reinventing America II report that FDA would allow companies to designate more than one person to act as the “Responsible Head” of manufacturing for a company.<sup>370</sup> FDA also proposed to further expedite the review of biologics by eliminating the requirement that promotional labeling for biologics be approved prior to use and by deciding within thirty days whether newly submitted information supported the continuation of a clinical trial that had been put on hold by FDA.<sup>371</sup>

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<sup>369</sup> See Michele L. Robinson, *FDA Circulates Draft to Equalize Regulation of Biotech Drugs*, BIOWORLD, vol. 6, No. 209, October 31, 1995 (available on-line as 1995 WL 14406660).

<sup>370</sup> *Id.* Implemented in Food and Drug Administration, *Revision of the Requirements for a Responsible Head for Biological Establishments*, 62 Fed.Reg. 53,536 (1997).

<sup>371</sup> Reinventing America II report, *supra*, note 12.

By late 1995, FDA had approved over thirty biotech products and almost two-hundred biotechnology products had reached advanced clinical trials.<sup>372</sup> FDA administrative reforms and use of funds provided from user fees had significantly reduced approval times and expanded early access to products prior to approval. However, the two NPR reports still resulted in a significant number of hearings before multiple House and Senate subcommittees regarding the status of FDA regulation, and these hearings ultimately inspired several proposals in Congress aimed at legislative reform of FDA.<sup>373</sup> The first of these legislative reform bills was the proposed FDA Modernization Act of 1995 (“H.R. 1742”), introduced in June of 1995.<sup>374</sup> Among the many provisions of the bill, H.R. 1742 proposed to allow “conditional approval” of new drugs and Class III medical devices intended to treat “life-threatening or serious health conditions” during the period in which a NDA or PMA application is pending, and the bill would

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<sup>372</sup>Biomedical Market Newsletter, *Biotech Products: Record Number Ready for FDA*, Vol. 5, No. 7 ISSN: 1064-4180 (available on-line as 1995 WL 8379209); Lauran Neergaard, *FDA Eases Rules for Biotech Drugs*, Associated Press, November 9, 1995 (available on-line as 1995 WL 4413545).

<sup>373</sup>These hearings included: FDA Approval Process, Hearing Before the Subcomm. on Health and the Environ. of the House Comm. on Commerce, 104th Cong., 2d Sess. (May 1, 1996); Need for Changes at the FDA, Hearing Before the Subcomm. on Oversight and Investigations of the House Comm. on Commerce, 104th Cong., 2d Sess. (Feb. 27, 1996); More Information for Better Patient Care, Hearing Before the Senate Comm. on Labor and Human Resources, 104th Cong., 2d Sess. (Feb. 22, 1996); Revitalizing New Product Development: From Clinical Trials Through FDA Review, Hearing Before the Senate Comm. on Labor and Human Resources, 104th Cong., 2d Sess. (Feb. 21, 1996); Effect of Regulations on Medical Technology Development, Hearing Before the Subcomm. on Technology of the House Comm. on Science, 104th Cong., 1st Sess. (Nov. 2, 1995); Elderly Access to Advance Medical Technologies, Hearing Before the Subcomm. on Aging of the Senate Comm. on Labor and Human Resources, 104th Cong., 1st Sess. (July 13, 1995); FDA Approval of Drugs, Hearing Before the Subcomm. on Oversight and Investigations of the House Comm. on Commerce, 104th Cong., 1st Sess. (May 25, 1995); Reform of the Food and Drug Administration, Hearing Before the Senate Labor and Human Resources Comm., 104th Cong., 1st Sess. (Apr. 5, 1995). From Pilot & Waldmann, *supra*, at fn. 32.

<sup>374</sup>H.R. 1742, 104<sup>th</sup> cong., 1<sup>st</sup> Sess. (June 6, 1995).

have required review of IND applications within 30 days.<sup>375</sup>H.R. 1742 also contained provisions that granted authority to, but did not require, FDA to certify private institutions to review aspects of 510(k) medical device “substantial equivalence” applications.<sup>376</sup>This bill further proposed to reform labeling and advertisement regulation by amending the definition of product “labeling” and “advertisement” to exclude the distribution of “scientifically valid” medical reports and research contained in journals and textbooks to doctors and medical insurance providers.<sup>377</sup>Additionally, H.R. 1742 proposed requiring FDA to issue new CGMP regulations stating that manufacturing changes to facilities producing only drug and biological products “which can be characterized adequately by physical or chemical methods” would not have to be pre-approved by FDA unless “such manufacturing changes are specified in regulations as substantially affecting the safety or efficacy of such drugs and biological products.”<sup>378</sup>H.R. 1742 further proposed to reclassify a large group of Class II medical devices as Class I devices.<sup>379</sup>

The second proposed legislative reform bill was the FDA Performance and Accountability Act of 1995 (“S. 1477”), sponsored by Senator Nancy Kasse-

<sup>375</sup>H.R. 1742 ♣♣ 4 (conditional approval), 5 (IND review).

<sup>376</sup>H.R. 1742 ♣ 6.

<sup>377</sup>H.R. 1742 ♣ 7(a).

<sup>378</sup>H.R. 1742 ♣ 9.

<sup>379</sup>H.R. 1742 ♣ 12.



baum.<sup>380</sup> S. 1477 proposed sweeping reforms and limitations to FDA regulation, in an attempt to significantly reduce the jurisdiction of FDA. First, S. 1477 proposed to redefine the “mission” of FDA to reemphasize the goal of rapid product approvals.<sup>381</sup> The bill would have required FDA to review all “standard” drugs within 180 days and all “priority” drugs within 120 days, without providing FDA with any additional resources in order to meet these deadlines.<sup>382</sup> S. 1477 also proposed allowing private institutions to review Class I and II medical device applications and some Class III devices.<sup>383</sup> Additionally, the bill proposed to significantly expand the 510(k) exemption to allow medical devices approved under existing 510(k) applications to be marketed for other indications, without regard to risk, with only the submission of an abbreviated 510(k) notice application.<sup>384</sup> S. 1477 also proposed that an unapproved use of a product could be advertised in the labeling of the product if experienced physicians had commonly prescribed the product for that unapproved use (called an “off-label use”) for a period of five years.<sup>385</sup>

The third major piece of proposed reform legislation was the Drugs and Biological Products Reform Act proposal of 1996 (“H.R. 3199”), sponsored by a bipartisan group of twelve members of Congress.<sup>386</sup> H.R. 3199 first proposed to

<sup>380</sup>S. 1477, 104<sup>th</sup> Cong., 1<sup>st</sup> Sess. (December 13, 1995) (amended and reintroduced June 20, 1996). *See also* Pilot & Waldmann, *supra*, note 91, at 271.

<sup>381</sup>S. 1477 ♣2 (redefining the “mission” of FDA to be” (1) facilitating the rapid and efficient development and availability of products subject to its regulation; (2) protecting the public from unsafe or ineffective products subject to its regulation; and (3) enforcing the applicable statutes and regulations in a timely, fair, consistent, and decisive manner.”).

<sup>382</sup>S. 1477 ♣204. *See* Kessler Testimony, *supra*, note 344.

<sup>383</sup>S. 1477 ♣743. *See also* Pilot & Waldmann, *supra*, note 91, at 272.

<sup>384</sup>S. 1477 ♣702. *See also* Kessler Testimony, *supra*, note 344.

<sup>385</sup>S. 1477 ♣407. *See also* Kessler Testimony, *supra*, note 344.

<sup>386</sup>H.R. 3199, 104<sup>th</sup> Cong., 2d Sess. (March 29, 1996).

redefine the “mission” of FDA as “[to] protect the public health and safety and promptly and efficiently review and approve clinical research and marketing of products in a manner that does not unduly impede innovation or product availability.”<sup>387</sup> H.R. 3199 also proposed to significantly reduce the volume of data from clinical trials required to be submitted by manufacturers to FDA.<sup>388</sup> Similar to the Kassebaum bill, H.R. 3199 contained a proposal to allow dissemination of scientific and medical research publications regarding off-label uses of drugs unless the manufacturer “in addition to disseminating the above-referenced [off-label] information, encourage[d] the unapproved use of a legally marketed drug or device through labeling, advertising, or other means of promotion.”

<sup>389</sup>In addition, H.R. 3199 proposed to require FDA to approve off-label uses of previously-approved drugs if “the new use is common and

3199 contained a proposal for mandatory accreditation of private institutions to conduct the review of medical device applications, and H.R. 3199 further proposed to allow such private institutions to conduct CGMP inspections as well.<sup>391</sup> The bill also contained proposals to allow pilot plants to receive ELA and PLA licenses and to relax the pre-approval requirements for manufacturing changes to facilities producing “well-characterized” drugs and biologicals.<sup>392</sup> Interestingly, the bill contained a proposal requiring FDA to establish an information system to track the status and progress of each pending application or

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<sup>387</sup>H.R. 3199 ♣2(b).

<sup>388</sup>H.R. 3199 ♣4(a). *See also* Henry J. Miller, *Failed FDA Reform*, REGULATION, v. 21, n. 3, p. 24-30, 1998, at 28.

<sup>389</sup>H.R. 3199 ♣20.

<sup>390</sup>H.R. 3199 ♣5(3).

<sup>391</sup>H.R. 3199 ♣ 8.

<sup>392</sup>H.R. 3199 ♣♣ 12 (pilot plants), 13 (well-characterized drugs and biologicals).

submission.<sup>393</sup>

None of these legislative reform proposals was ultimately adopted. However, the provisions contained within these initial reform proposals, in combination with the changes proposed by FDA in the Reinventing America I and II reports, formed the basis of reform legislation adopted the following year. The authorization for FDA to collect user fees was set to expire in October of 1997, and the necessity for reauthorization proved sufficient to force a legislative compromise.

This compromise was embodied in the FDA Modernization Act of 1997 (the “1997 Act”).<sup>394</sup> The 1997 Act incorporated and expanded upon many of the existing regulatory and legislative reform proposals.<sup>395</sup> First, the 1997 reauthorized the authority of FDA to collect user fees for an additional five years, with slight modifications to the user fees structure and administration.<sup>396</sup> As in 1992, in exchange for the authorization of user fees, the 1997 Act required a new set of even more aggressive performance milestones. These milestones, proposed separately from the 1997 Act, included decreasing the review times for “standard” applications to ten months, two months faster than the goal set in 1992, and maintaining the review time for “priority” applications at six months, as required in 1992.<sup>397</sup> Following the examples of S. 1477 and H.R. 3199,

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<sup>393</sup>H.R. 3199 §16.

<sup>394</sup>Pub. L. No. 105-115, 111 Stat. 2,296 (Nov. 21, 1997).

<sup>395</sup>See generally, Michael A. Friedman, M.D., Acting Commissioner, Food and Drug Administration, *Statement Before the Committee on Commerce, United States House of Representatives*, October 7, 1998 (available on-line at [www.fda.gov](http://www.fda.gov)).

<sup>396</sup>*Id.* at §§ 101-107, 111 Stat. 2,297, codified at 21 U.S.C.A. § 379.

<sup>397</sup>*Id.* at § 101(4), 111 Stat. 2,298.

the 1997 Act redefined the “mission” of FDA as “[to] promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner”, and the 1997 Act additionally required FDA to issue a detailed annual report of its progress in reaching compliance with the provisions of the 1997 Act.<sup>398</sup> Expanding upon FDA’s prior administrative reform announced in the Reinventing Government II report of allowing a single application in place of the ELA and PLA applications for “well-characterized” biologics, the 1997 Act unified the ELA and PLA license requirement into a single Biologics License Application (BLA) for all biologics, without regard to their status as “well-characterized”.<sup>399</sup> The 1997 Act contained provisions allowing data collected from a pilot plant to be used to demonstrate the safety and effectiveness of a new drug, extending into the drug context FDA’s Reinventing Government II proposal to allow approvals for biologics based upon data derived from pilot plants.<sup>400</sup> The 1997 Act also required FDA to implement “an information system to track the status and progress of each application or submission”, as had been suggested in H.R. 3199.<sup>401</sup> The 1997 Act codified FDA’s proposal from the Reinventing America I report that a single adequate and well-controlled clinical trial could, in some cases, be sufficient to support an NDA application, a reform which FDA had already begun to implement administratively.<sup>402</sup> However, the 1997 Act tempered this

<sup>398</sup>1997 Act §§ 407(a)-(b) (mission), (g) (annual report), 111 Stat. 2369, codified at 21 U.S.C.A. §393.

<sup>399</sup>1997 Act § 123, 111 Stat. 2,322, codified at 21 U.S.C.A. § 262.

<sup>400</sup>1997 Act § 124, 111 Stat. 2,324, codified at 21 U.S.C.A. § 355.

<sup>401</sup>§ 407, 111 Stat. 2,370.

<sup>402</sup>§ 115(a), 111 Stat. 2,312, codified at 21 U.S.C.A. § 355 (“If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investiga-

reform by preserving the presumption that the majority of applications for new products would still require at least two clinical trials in order to obtain adequate data to demonstrate safety and effectiveness.<sup>403</sup>

The 1997 Act expanded the trial program of private institutional review of medical device applications to which FDA had originally agreed in the Reinventing

America I report. <sup>404</sup>*Under the 1997 Act, FDA was required to begin accrediting private institutions within one year of adoption of*

Private institutional reviewers were authorized both to review 510(k) “substantial equivalence” applications for specified Class I and Class II medical devices and to make recommendations to FDA regarding the appropriate initial classification of devices.<sup>406</sup> The 1997 Act set an outer limit to the private review system, however, prohibiting private institutions from reviewing any Class III medical device or any Class II medical device that either was “intended to be permanently implantable or life sustaining or life supporting” or “require[d] clinical data in the report submitted under section 510(k)”.<sup>407</sup> The 1997 Act also granted FDA’s request in the Reinventing America I report for authorization to collect user fees to support the system of private institutional review of medical devices.<sup>408</sup>

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tion and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of [product approval].”).

<sup>403</sup>Food and Drug Administration, Department of Health and Human Services, *Food and Drug Administration Modernization Act Background*, 97-13 (1997) (available on-line at [www.fda.gov](http://www.fda.gov)).

<sup>404</sup>1997 Act § 210, 111 Stat. 2,341, codified at 21 U.S.C.A. § 360(m).

<sup>405</sup>*Id.* at § 210(a)(1).

<sup>406</sup>*Id.*

<sup>407</sup>1997 Act § 210(a)(3), 111 Stat. 2,342, codified at 21 U.S.C.A. § 360(m).

<sup>408</sup>*Id.* at § 210(b)(5) (“Compensation for an accredited person shall be determined by agreement between the accredited person and the person who engages the services of the accredited person, and shall be paid by the person who engages such services.”).

The 1997 Act contained provisions containing reforms to FDA regulation of off-label uses.<sup>409</sup> The off-label reform provisions contained in the 1997 Act struck a balance between the highly-restricted role of FDA in regulating off-label uses under the H.R. 3199 and S. 1477 proposals and FDA's traditional requirement that all such off-label uses be pre-approved under a supplemental NDA application. Under these provisions, a manufacturer could distribute written information concerning the safety, effectiveness, and benefits of a use not described in the approved labeling of a drug or device if the drug or device was already approved by FDA for a separate use, the manufacturer had submitted a supplemental NDA application to cover the intended use or had certified that it intended to submit such an application, the materials to be distributed contained a statutorily-prescribed warning and disclosure statement, and the manufacturer submitted to FDA at least sixty days prior to any such proposed distribution both the written materials to be distributed and "any clinical trial information the manufacturer ha[d] relating to the safety or effectiveness of the new use, any reports of clinical experience pertinent to the safety of the new use, and a summary of such information".<sup>410</sup> The written materials to be so distributed could consist only of unabridged peer reviewed articles "considered to be scientifically sound" or unabridged "reference publications" and could only

<sup>409</sup> ♣ 401(a), 111 Stat. 2,357, codified at 21 U.S.C.A. ♣ 360aaa. *See generally*, Food and Drug Administration, Department of Health and Human Services, *FDA Proposes Rules for Dissemination of Information on Off-Label Uses*, HHS News (available on-line at [www.fda.gov](http://www.fda.gov)). FDA implemented these provisions in Food and Drug Administration, *Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices*, 63 Fed.Reg. 64,555 (Nov. 20, 1998).

<sup>410</sup> ♣ 401(a), 111 Stat. 2,357, codified at 21 U.S.C.A. ♣ 360aaa.

be distributed so long such materials were “not false or misleading and would not pose a significant risk to the public health.”<sup>411</sup> Additionally, such written materials could only be distributed to health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, and Federal or State governmental agencies.<sup>412</sup>

The 1997 Act contained an extensive set of reforms to designed to expedite the FDA review process and allow seriously-ill patients early access to novel therapies prior to completion of the entire FDA review process. First, the 1997 Act required that FDA “facilitate the development and expedite the review of [a new] drug if it is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition”, which essentially codified the accelerated approval process; the 1997 Act refers to such accelerated new drugs as “fast track products”.<sup>413</sup> The 1997 Act required FDA to review applications for fast track treatment of new products within sixty days.<sup>414</sup> The fast track provisions also codified FDA’s existing practice of approving NDA applications based upon evidence that a product had an effect on a surrogate endpoint.<sup>415</sup> Second, the 1997 Act

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<sup>411</sup> *Id.* at 2,358. A “reference publication” was defined as “a publication that (1) has not been written, edited, excerpted, or published specifically for, or at the request of, a manufacturer of a drug or device; (2) has not been edited or significantly influenced by such a manufacturer; (3) is not solely distributed through such a manufacturer but is generally available in bookstores or other distribution channels where medical textbooks are sold; (4) does not focus on any particular drug or device of a manufacturer that disseminates information under [the off-label reform provisions] . . . and does not have a primary focus on new uses of drugs or devices that are marketed or under investigation by a manufacturer supporting the dissemination of information; and (5) presents materials that are not false or misleading.” (*Id.* at 2,359).

<sup>412</sup> *Id.* at 2,357.

<sup>413</sup> ♣ 112(a), 111 Stat. 2,309, codified at 21 U.S.C.A. ♣ 356. See Friedman, *supra*, note 391.

<sup>414</sup> *Id.*

<sup>415</sup> ♣ 112(b), 111 Stat. 2,309, codified at 21 U.S.C.A. ♣ 356. See Friedman, *supra*, note 391.

codified reforms to the IND process. Manufacturers had complained that the disclosure and paperwork requirements necessary to institute a clinical trial were excessively burdensome and that, once a trial was finally initiated, the clinical hold procedures available to FDA to stop such a trial granted excessive administrative discretion to FDA. To streamline the IND application process, the 1997 Act reduced the information required to be disclosed to FDA prior to initiation of the IND process and stated that a manufacturer could begin the IND process thirty days after filing this required information with FDA.<sup>416</sup> To address the complaints regarding the discretion of FDA to place a clinical trial on hold, the 1997 Act allowed FDA to institute a clinical hold only if it first determined that “the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation” and then required FDA to place the reasons for this determination in writing.<sup>417</sup>

Third, the 1997 Act codified the exiting treatment IND procedures, originally proposed administratively by FDA in the IND Rewrite. These provisions authorized FDA to allow manufacturers to conduct treatment INDs for “investigational drugs or investigational devices for the diagnosis, monitoring, or treatment of a serious disease or condition in emergency situations.”<sup>418</sup> For treatment INDs involving multiple patients, termed “expanded access protocols” under the 1997 Act, these provisions required FDA to approve a treatment IND application if the product was intended to treat a “serious or immediately life-

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<sup>416</sup> ♣ 117, 111 Stat. 2,315, codified at 21 U.S.C.A. ♣ 355.

<sup>417</sup> *Id.*

<sup>418</sup> ♣ 402, 111 Stat. 2,365, codified at 21 U.S.C.A. ♣ 360bbb.



threatening disease or condition” and was already the subject of clinical trials in the general IND process, the manufacturer was pursuing approval in these general trials with “due diligence”, “no comparable or satisfactory alternative therapy” existed, and there was either, in the case of serious diseases, “sufficient evidence of safety and effectiveness to support the use described [in the IND application]” or, in the case of immediately life-threatening diseases, “the available scientific evidence, taken as a whole, provide[d] a reasonable basis to conclude that the [product] may be effective for its intended use and would not expose patients to an unreasonable and significant risk of illness or injury.”<sup>419</sup>The 1997 Act provisions also allowed individual patients to be the subject of a treatment IND.<sup>420</sup>As early as 1968, FDA had informally allowed individual patients that could not participate in larger clinical trials to access investigational products in a separate single patient protocol, often called a “compassionate use” study.<sup>421</sup>The 1997 Act codified this informal practice, allowing single patient INDs if a “licensed physician determine[d] that the person ha[d] no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat the disease or condition involved”, “the probable risk to the person from the [product] [wa]s not greater than the probable risk from the disease or condition”, “sufficient evidence of safety and effectiveness to support the [investigational] use” existed, the single patient IND would “not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval”, and the product

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<sup>419</sup> ♣ 402(c), 111 Stat. 2,367, codified at 21 U.S.C.A. ♣360bbb.

<sup>420</sup> ♣ 402(b), 111 Stat. 2,365-6, codified at 21 U.S.C.A. ♣360bbb.

<sup>421</sup>Friedman, *supra*, note 391.

manufacturer consented and filed a clinical protocol for the single patient IND study.<sup>422</sup> These provisions also authorized FDA's existing practice of allowing "emergency INDs", which are single patient INDs intended to treat emergency illnesses in which the treating physician did not have sufficient time, prior to the initiation of treatment, to file the required treatment IND paperwork with FDA; in practice, FDA had authorized the majority of these emergency uses of investigational products over the phone within a few hours of the treating physician's request.<sup>423</sup>

## VI. Conclusion

The administrative and legislative reforms during the 1980s and 1990s resulted in a streamlined and highly-efficient regulatory framework for products of biotechnology. FDA review times for biotechnology products were comparable to or only slightly longer than those of its counterparts in Europe for general applications, and FDA review times were significantly faster for priority applications.<sup>424</sup> A survey of biotechnology industry executives, released at the BIO 2000 Conference in Boston, found a high level of industry satisfaction with the changes to FDA regulatory review of the products of biotechnology.<sup>425</sup> FDA has also continued to maintain both its position as the key regulator of the

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<sup>422</sup> ♣ 402(b), 111 Stat. 2,365-6, codified at 21 U.S.C.A. ♣360bbb.

<sup>423</sup> *Id.* Friedman, *supra*, note 40.

<sup>424</sup> MARKETLETTER, *EMEA Approvals of New Biotech Drugs Faster than US FDA, Says Tufts Study*, April 3, 2000 (available on-line as 2000 WL 7541236). ("The total review times during 1995-99 were for companies based in: Denmark - 386 days; Germany - 414 days; USA - 450 days; Netherlands - 488 days; and Switzerland - 507 days... [and] FDA approval times are considerably faster than the EMEA's for priority products).

<sup>425</sup> Thomas Kupper, *Biotechs say FDA Services Improve*, SAN DIEGO UNION-TRIBUNE, March 29, 2000 (available on-line as 2000 WL 13956301).

biotechnology products and its central role in the regulation of biotechnology research generally.

An example of the significant role of FDA regulation of biotechnology at the end of the century came when, in February of 1997, scientists at the Roslin Institute in Scotland announced that they had successfully cloned an entire sheep, producing an exact genetic replica of its mother.<sup>426</sup> This announcement sparked intense public debate concerning the potential implications of cloning humans.<sup>427</sup> These concerns led President Clinton to stop all federal funding for research involving the cloning of humans.<sup>428</sup> President Clinton directed the National Bioethics Advisory Commission (NBAC) to analyze the legal and ethical implications of human cloning, and, three months later, the NBAC recommended that Congress adopt legislation banning all such research.<sup>429</sup> Legislation was proposed at both the state and federal levels to ban research involving human cloning.<sup>430</sup> Though some of the state legislative proposals were adopted, federal

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<sup>426</sup> See Ian Wilmut, *Dolly's False Legacy*, TIME, January 11, 1999.

<sup>427</sup> *Id.*

<sup>428</sup> President Clinton, *Memorandum on the Prohibition on Federal Funding for Cloning of Human Beings*, 33 WEEKLY COMP. PRES. DOC. 281 (Mar. 4, 1997); President Clinton, *Speech Regarding the Prohibition on Federal Funding for Cloning of Human Beings*, 33 Weekly Comp. Pres. Doc. 281 (Mar. 4, 1997). See Elizabeth C. Price, *Does the FDA Have Authority to Regulate Human Cloning?*, 11 HARV. J.L. & TECH. 619, 623 (Summer 1998).

<sup>429</sup> National Bioethics Advisory Commission, *Cloning Human Beings: Report and Recommendations of the National Bioethics Advisory Commission*, at 15-16 (1997). See also Gregory J. Rokosz, *Human Cloning: Is the Reach of FDA Authority Too Far A Stretch?*, 30 Seton Hall L. Rev. 464, 465 (2000).

<sup>430</sup> See Rokosz, *supra*, note 70, fn. 9, 14 (citing S. 511, 1997 Leg., Reg. Sess. (Ala. 1997); A.B. 1082, 1997 Leg., Reg. Sess. (Ala. 1997); S.J.R. 14, 1997-98 Leg., 1st Sess. (Cal. 1997); S.C.R. 39, 1997-98 Leg., 1st Sess. (Cal. 1997); S. 1344, 1997-98 Leg., 1st Sess. (Cal. 1997) (enacted); A.B. 1251, 1997-98 Leg., 1st Sess. (Cal. 1997); H.B. 1237, 1997-98 Leg., 1st Sess. (Fla. 1997); H.B. 2235, 90th Leg., 1st Sess. (Ill. 1997); H.B. 1829, 90th Leg., 1st Sess. (Ill. 1997); S. 134, 118th Leg., 1st Sess. (Me. 1997); H.J.R. 28, 1997-98 Leg., 1st Sess. (Md. 1997); H.B. 4846, 89th Leg., 1st Sess. (Mich. 1997); H.B. 4962, 89th Leg., 1st Sess. (Mich. 1997); H.B. 824, 89th Leg., 1st Sess. (Mo. 1997); A.B. 2849, 207th Leg., Reg. Sess. (N.J. 1997); S. 2877, 220th Leg., Reg. Sess. (N.Y. 1997); A.B. 5383, 220th Leg., Reg. Sess. (N.Y. 1997); S. 782, 1997-98 Leg., 1st Sess. (N.C. 1997); S. 1017, 69th Leg., 1st Sess. (Or. 1997); H.B. 3617, 112th Leg., 1st Sess. (S.C. 1997); S. 410, 73rd Leg., 1st Sess. (W. Va. 1997); S.

legislation banning human cloning experiments was not passed.<sup>431</sup> This Congressional inaction meant that, although no public funds could be utilized to conduct human cloning research, there existed no prohibition upon private research involving the cloning of humans.

Amidst this debate, in early 1998, a Chicago physicist announced that he would attempt to clone humans using private funding sources.<sup>432</sup> In response, Secretary of Health and Human Services Donna Shalala announced her opposition to this private research project, and, shortly thereafter, the President of the Biotechnology Industry Organization sent a letter to Secretary Shalala, copied to FDA Commissioner Friedman, requesting that FDA regulate all research involving human cloning.<sup>433</sup>

One week later, FDA announced its intention to regulate research involving human cloning and to prosecute any person conducting such research without receiving prior approval from FDA.<sup>434</sup> Some commentators have questioned

whether FDA's administrative jurisdiction will actually extend to the regula-

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1574, 105th Cong. (1998); S. 1599, 105th Cong. (1998); S. 1601, 105th Cong. (1998); S. 1602, 105th Cong. (1998); S. 1611, 105th Cong. (1998); H.R. 3133, 105th Cong. (1998)).

<sup>431</sup> See B. Jason Erb, *Deconstructing the Human Egg: The FDA's Regulation of Scientifically Created Babies*, 5 Roger Williams U. L. Rev. 273, 274-5 (Fall 1999).

<sup>432</sup> See Wendy Cole, *Seed of Controversy*, TIME, January 11, 1999.

<sup>433</sup> Secretary Shalala's announcement was made on the CBS television show "Face the Nation", on January 11, 1998; Letter from Carl B. Feldman, President, Biotechnology Industry Organization to The Honorable Donna E. Shalala, Secretary, Department of Health & Human Services, (Jan. 13, 1998) (on file with the Harvard Journal of Law & Technology). Price, *supra*, note 424 at 623-4.

<sup>434</sup> See Rick Weiss, *Human Clone Research Will Be Regulated; FDA Asserts It Has Statutory Authority To Regulate Attempts at Human Cloning*, WASHINGTON POST, Section A1, Jan. 20, 1998 (available on-line as 1998 WL 2462936) ("Through the Food, Drug and Cosmetic Act we do have the authority to regulate human cloning, and we are prepared to assert that authority," acting FDA Commissioner Michael A. Friedman said in an interview.). F.D.C. Reports, 60 The Pink Sheet No. 3, Jan. 19, 1998 at T&G1.

tion of human cloning if challenged in court, however, FDA already regulated genetic modification of cellular and tissue-based products, transfers of recombinant DNA into human subjects, and human somatic-cell gene therapies, and human cloning experiments incorporated aspects of each of these areas of research.<sup>435</sup>

FDA's expertise in the regulation of biotechnology, its high level of interaction with industry participants, and its ability to respond rapidly to scientific advances and discoveries have placed FDA in an ideal position to regulate the products of biotechnology. FDA's reforms and administrative initiatives instituted during the twentieth century have created a framework of regulation that will ensure that the public remains safeguarded from potential medical hazards while review and approval of novel products of biotechnology produced in the years to come are not unduly delayed.

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<sup>435</sup>Food and Drug Administration, *Proposed Approach to Regulation of Cellular and Tissue-Based Products*, 62 Fed. Reg. 9,721 (March 4, 1997); Food and Drug Administration, *Recombinant DNA Research: Request for Public Comment on Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA into Human Subjects*, 54 Fed. Reg. 266,660 (June 23, 1989); Food and Drug Administration, *Recombinant DNA Research; Request for Public Comment on Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols*, 54 Fed. Reg. 10,956 (March 15, 1989). For commentator analyses of FDA administrative jurisdiction over human cloning, see e.g. Weiss, *supra*, note 430; Price, *supra*, note 424; Erb, *supra*, note 427; Rokosz, *supra*, note 425.