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Managing Biotechnology's [R]evolution: *Has Guarded Enthusiasm Become Benign Neglect?*

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ABSTRACT

Several commentators have emphasized the distinctiveness of "biotechnology" and the consequent need for appropriately tailored responses by legal institutions. After initially identifying the imprecise boundaries of the field, this Article gauges such assessments by reviewing several therapeutic, agricultural, and other industrial applications of biotechnology. Because this is not a monolithic enterprise, our multifaceted regulatory response reflects the potentially vast and varied reach of these innovative techniques. Biotechnology has ushered in profound changes at some levels (and may require special attention from regulators), but, in other respects, it has shown remarkable continuity with the techniques that preceded it. Legal institutions must try to avoid getting blinded by the hype and inappropriately sweeping in – and perhaps overregulating – both the novel and the mundane applications of this still relatively young science and newer ones (such as nanotechnology) just on the horizon.

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A. Defining the Field and Assigning Regulatory Jurisdiction

¶ 1 The term "biotechnology" gets bandied about a good deal, but its precise meaning remains somewhat elusive. Dictionaries provide a sense for this ambiguity. For instance, the *Oxford English Dictionary* offers both a broad definition of older vintage ("The branch of technology concerned with the development and exploitation of machines in relation to the various needs of human beings") as well as a narrower and newer definition ("The branch of technology concerned with modern forms of industrial production utilizing living organisms, esp. micro-organisms, and their biological processes"),[1] which the *American Heritage Dictionary* provides as the sole definition.[2]

1. *See* II OXFORD ENGLISH DICTIONARY 210 (2d ed. 1989). Even the narrower definition may sweep too broadly insofar as it might encompass conventional techniques such as brewing alcohol and making cheese. *Cf.* OXFORD DICTIONARY OF SCIENCE 92 (2003) (explicitly defining biotechnology to include cheese and wine making).

2. *See* AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE 185 (4th ed. 2000) ("The use of microorganisms, such as bacteria or yeasts, or biological substances, such as enzymes, to perform specific industrial or manufacturing processes. Applications include the production of certain drugs, synthetic hormones, and bulk foodstuffs as well as the bioconversion of organic waste and the use of genetically altered bacteria in the cleanup of oil spills."); *see also* CONCISE OXFORD ENGLISH DICTIONARY 136 (11th ed. 2004) ("The exploitation of biological processes for industrial or other purposes, especially the genetic manipulation of microorganisms for the production of antibiotics, hormones, etc."); U.S. CONG., OFFICE OF TECH. ASSESSMENT, NEW DEVELOPMENTS IN BIOTECHNOLOGY: PATENTING LIFE 3 (1989)

Webster's provides a still narrower meaning of the term: "biological science when applied especially in genetic engineering and recombinant DNA technology."[3]

¶ 2 Common usages of the term "biotechnology" also reflect this range of possible meanings. For instance, the President's Council on Bioethics (PCB) recently issued a report expressing concerns about potential adverse consequences of biotechnological interventions that lack a therapeutic purpose, which it took to include such disparate things as sex selection, lifespan extension, and conventionally produced drugs intended to enhance the body or mind,[4] but this usage conflates biotechnology and biomedical technology.[5] Conversely, other technophobes may focus on its more controversial core,

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(defining 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 microorganisms for specific uses").

3. WEBSTER'S NEW ENCYCLOPEDIC DICTIONARY 179 (2002); *see also* WEBSTER'S UNABRIDGED DICTIONARY 211 (2d ed. 2001) ("The use of living organisms or other biological systems in the manufacture of drugs or other products or for environmental management, as in waste recycling: includes the use of bioreactors in manufacturing, microorganisms to degrade oil slicks or organic waste, genetically engineered bacteria to produce human hormones, and monoclonal antibodies to identify antigens."). Earlier definitions swept more broadly. *See* WEBSTER'S NEW WORLD COLLEGE DICTIONARY 147 (4th ed. 1999) ("the use of the data and techniques of engineering and technology for the study and solution of problems concerning living organisms"); WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY 219 (unabridged 1986) (defining the term simply as "applied biological science (as the synthesis of enzymes, genes, and antibodies for medical use)").

4. *See* Nicholas Wade, *Bush's Advisers on Biotechnology Express Concern on Its Use*, N.Y. TIMES, Oct. 17, 2003, at A18; *see also* PRESIDENT'S COUNCIL ON BIOETHICS, BEYOND THERAPY: BIOTECHNOLOGY AND THE PURSUIT OF HAPPINESS 1 & n.i (2003), *available at* http://www.bioethics.gov/reports/beyondtherapy/index.html (last visited July 14, 2006); Rick Weiss, *Conservatives Draft a "Bioethics Agenda" for President*, WASH. POST, Mar. 8, 2005, at A6 (quoting a document co-authored by PCB chair Leon Kass: "We have today an administration and a Congress as friendly to human life and human dignity as we are likely to have for many years to come. . . . It would be tragic if we failed to take advantage of this rare opportunity to enact significant bans on some of the most egregious biotechnical practices."). *See generally* SHELDON KRIMSKY, BIOTECHNICS AND SOCIETY: THE RISE OF INDUSTRIAL GENETICS (1991); John B. Attanasio, *The Genetic Revolution: What Lawyers Don't Know*, 63 N.Y.U. L. REV. 662 (1988) (book review); Rochelle Cooper Dreyfuss & Dorothy Nelkin, *The Jurisprudence of Genetics*, 45 VAND. L. REV. 313 (1992); Jonathan Kahn, *Biotechnology and the Legal Constitution of the Self: Managing Identity in Science, the Market, and Society*, 51 HASTINGS L.J. 909 (2000).

5. The Convention on Biological Diversity broadly defines the term "biotechnology" as "any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific uses." Thomas P. Redick et al., *Private Legal Mechanisms for Regulating the Risks of Genetically Modified Organisms: An Alternative Path Within the Biosafety Protocol*, 4 ENVTL. L. 1, 5 n.3 (1997) (citation omitted); *cf. id.* at 25-26 & n.161 (discussing South African biotechnology legislation that covers only rDNA techniques and specifically excludes a number of related genetic modification methods); Jeffrey K. Francer, Note, *Frankenstein Foods or Flavor Savers?: Regulating Agricultural Biotechnology in the United States and European Union*, 7 VA. J. SOC. POL'Y & L. 257, 261 & n.21 (2000) (observing that "even a definition of the term 'biotechnology' may elude agreement," and noting that "forty-one different definitions of biotechnology coexisted within various European community documents"). *See generally* Sean D. Murphy, *Biotechnology and International Law*, 42 HARV. INT'L L.J. 47 (2001) (discussing the importance of resolving fundamental disagreements). Under the terms of the Convention, several countries signed the Cartagena Protocol on Biosafety, 39 I.L.M. 1027 (2000), though implementation issues remain. *See* Michael P. Healy, *Information Based Regulation and International Trade in Genetically Modified Agricultural Products: An Evaluation of the Cartagena Protocol on Biosafety*, 9 WASH. U. L.J. & POL'Y 205 (2002); Andrew Pollack, *130 Nations Agree on Safety Rules for Biotech Food*, N.Y. TIMES, Jan. 30, 2000, § 1, at 1. The Protocol governs any "living modified organism" (LMO), which Article 3(g) defines as "any living organism that possesses a novel combination

treating biotechnology as synonymous with the use of genetically modified (GM) organisms (GMOs or "transgenics") as distinct from what some might call old-fashioned biotechnological methods such as cross-breeding,[6] though even that line can blur – before rDNA techniques became available, plant breeders might use mutagenesis, inducing random mutations with chemicals or radiation and then hoping to discover some desirable characteristics in the progeny. Perhaps one can draw a distinction between the older (more "natural") processes and the newer ("artificial") techniques, reserving the label "biotechnology" for the latter category.[7]

¶3 Entrepreneurs (technophiles) looking for venture capital or deals with potential investors – or to secure patent protection, which requires a showing of novelty – may seek to appropriate the once and still fashionable "biotechnology" moniker to characterize their plans.[8] In 2004, the shortage of flu vaccine drew public attention to the

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of genetic material obtained through the use of modern biotechnology," which in turn Article 3(i) defines to include laboratory methods for introducing novel DNA into cells that "overcome natural physiological reproductive or recombinant barriers" to the exchange of genetic material, but Article 5 excludes human pharmaceuticals. *See* Paul E. Hagen & Jonathan Barlow Weiner, *The Cartagena Protocol on Biosafety: New Rules for International Trade in Living Modified Organisms*, 12 GEO. INT'L ENVTL. L. REV. 697, 702-03 (2000) (discussing these provisions).

6. *See infra* notes 227-28 and accompanying text (discussing public interest groups opposed to biotechnology); *see also* Jonathan H. Adler, *More Sorry Than Safe: Assessing the Precautionary Principle and the Proposed International Biosafety Protocol*, 35 TEX. INT'L L.J. 173, 176 (2000) (explaining that "the term [biotechnology] is generally used to refer to newer biotechnology techniques, particularly the use of recombinant DNA (rDNA) techniques to modify organisms at the genetic level"); Lewis Thomas, *Overview: Regulating Biotechnology*, 3 YALE L. & POL'Y REV. 309, 310-11 (1985) (bemoaning the use of the "eye-catching, bragging metaphor" of "genetic engineering," and expressing apprehension about "what the public perception of hazard may do to the future prospects for basic research").

7. *See* Francer, *supra* note 5, at 262 ("While biotechnology, in the broad sense of the term, has been a part of food production for ages, it is the so-called 'new biotechnology' that evokes the most controversy."); Cass R. Sunstein, *Is Nature Good?*, NEW REPUBLIC, Oct. 23, 2000, at 35 (book review). One commentator usefully described a pair of "fundamentally different conceptions of GM technology," which he labeled "the Frankenstein and the Better Living through Chemistry narratives." John S. Applegate, *The Prometheus Principle: Using the Precautionary Principle To Harmonize the Regulation of Genetically Modified Organisms*, 9 IND. J. GLOBAL LEGAL STUD. 207, 208 (2001); *see also id*. at 228-40 (mapping the different regulatory approaches of the European Union and United States onto these distinctive templates); *id*. at 258-61 (offering the Prometheus myth as an alternative narrative, and the precautionary principle as an alternative regulatory approach, and concluding that "[t]he challenge is not in the technology itself, but in the care with which we use the technology, and in our ability to resist the lure of profit without considering consequences"). For a more general critique of the "better living through chemistry" mentality (a slogan borrowed from a well-known advertising campaign by DuPont), see James E. Krier & Clayton P. Gillette, *The Un-Easy Case for Technological Optimism*, 84 MICH. L. REV. 405 (1985).

8. *Cf.* Michael J. Malinowski, *Globalization of Biotechnology and the Public Health Challenges Accompanying It*, 60 ALB. L. REV. 119, 119-20 (1996) (observing that the industry has "drawn billions of investment funds from the private sector in a remarkably brief period of time"); *id*. at 155 & n.182 (describing the perhaps misplaced "public excitement over the prospects of biotechnology"); Tricia Bishop, *For Biotechs, Guarding Concepts Is Critical*, BALT. SUN, Apr. 30, 2006, at 4C; Denise Gellene, *Lure of Products Leads Drug Firms to Biotechs*, L.A. TIMES, June 23, 2005, at C1 ("[B]ig drug makers aren't just negotiating product deals but are snapping up biotech companies themselves. There have been 16 acquisitions of biotech companies by drug companies this year, compared with three during the first six months of 2004 . . . ."); Justin Gillis, *But Biotechnology Bucks the Trend*, WASH. POST, Dec. 30, 2005, at D2.

antiquated method of producing this product (namely, incubating strains of the influenza virus in specially purified, fertilized chicken eggs as the first step in deriving the vaccine) coupled with calls for more efficient "biotechnology" approaches (namely, infecting cell cultures with the virus and then multiplying these cells in fermentation tanks).[9] Absent a genetic modification, however, the biotechnology label appears to rest on the use of living organisms in the production process, but then it seems that the label would apply with equal justification to the much older chicken egg method or, indeed, all types of vaccines.

¶ 4 Scientists also may have ulterior motives for embracing the term "biotechnology," hoping to attract grants to support their work.[10] More recently, and in a similar vein, "researchers in search of funding have tended to define 'nanotechnology' rather broadly, including such things as molecular electronics and even high-resolution photolithography."[11]

> [A]s with any new technology, nanotechnologies are defined officially by the community of people who would like to be funded and by the people who are funding them. The broader definition now in use has nothing to do with atomic precision or molecular machinery . . . . It merely requires that some part of the thing in question be small, less than 100 nanometers in some significant dimension. Molecules have always been small, so chemistry is now called nanotechnology. Biomolecules are small, so biotechnology is being relabeled as nanotechnology.[12]

Indeed, the broader usages of the term biotechnology would encompass many genuinely innovative advances in the emerging field of nanomedicine,[13] but this Article treats

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9. *See* Rosie Mestel, *Chasing a Stealthy Influenza Virus*, L.A. TIMES, July 25, 2005, at F1; Michael S. Rosenwald, *Flu Crisis Sparks Fresh Look at Vaccine Production*, WASH. POST, Nov. 27, 2004, at A1 (reporting that "federal health officials are encouraging several biotech companies to develop cell-based vaccines," with an HHS spokesman conceding that "[t]here's a bit of a 'cool' factor at work here"); *see also* Paul Elias, *Still No Vaccine for Hype*, PHILA. INQUIRER, Dec. 5, 2005, at C3 (reporting that biotech companies have begun flocking to avian flu research); *cf.* Joseph Earley, Note, *Can Biotechnology Immunize Vaccine Manufacturers from the Products Liability Crisis?*, 30 JURIMETRICS J. 351, 352 & n.13, 362-67 (1990) (differentiating between conventional and biotech-derived vaccines). *See generally* Lars Noah, *Triage in the Nation's Medicine Cabinet: The Puzzling Scarcity of Vaccines and Other Drugs*, 54 S.C. L. REV. 741 (2003). For instance, the hepatitis B vaccine uses a protein produced through rDNA processes.

10. *See, e.g.*, Phil B. Fontanarosa & Catherine D. DeAngelis, Editorial, *Medical Applications of Biotechnology*, 293 JAMA 866, 866-67 (2005) (including genomics, proteomics, tissue engineering, stem cell research, and bioimaging techniques under the biotechnology banner, and calling for "substantial financial and policy support").

11. Glenn Harlan Reynolds, *Nanotechnology and Regulatory Policy: Three Futures*, 17 HARV. J.L. & TECH. 179, 190-91 (2003); *cf.* Lars Noah, *A Postmodernist Take on the Human Embryo Research Debate*, 36 CONN. L. REV. 1133, 1153, 1157-60 (2004) (suggesting that researchers embrace broad or narrow meanings of a term – or instead opt for euphemisms – depending on the prevailing political winds and possible regulatory ramifications).

12. K. Eric Drexler & Jason Wejnert, *Nanotechnology and Policy*, 45 JURIMETRICS J. 1, 19 (2004).

13. "Synthetic biology," which includes efforts to create DNA using artificial base pairs and to construct entirely new chromosomes, provides one illustration of this cross-over between biotech and nanotech. *See* Philip Ball, *Starting from Scratch*, 431 NATURE 624, 625 (2004); Bernadette Tansey,

recombinant DNA (a.k.a. "gene splicing") and similar genetic engineering techniques as representing the core of modern biotechnology, reserving a separate discussion of nanotechnology for Part III.

¶5 Conversely, regulatory officials anxious to deploy their existing delegations of authority may contend that the fruits of biotechnology fit within statutory definitions enacted in an earlier era.[14] Then, when agencies purport to act within their jurisdiction and announce the types of activities that they intend to subject to closer scrutiny, regulated entities may seek to narrow the definition or downplay the distinctiveness of their products.[15] For instance, the Food and Drug Administration (FDA) has formulated rules that would subject "more than minimally manipulated" human tissue and cellular products to the full panoply of rules governing drugs, devices, or biologics,[16] which would encourage regulated entities to argue that their manipulations did not exceed this ill-defined *de minimis* threshold.[17] Again, a similar tendency already has appeared in the

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Science Tweaks Nature's Toolbox: Latest Genetic Engineering Uses Living Organisms, S.F. CHRON., Aug. 20, 2005, at C1; *see also* Andrew Pollack, *Live from the Lab, a Culture Worth a Thousand Words*, N.Y. TIMES, Nov. 24, 2005, at A30 ("[T]he distinction between synthetic biology and more conventional genetic engineering is not always clear."). Moreover, nanotechnology partially emerged from biotechnology and may continue to depend on its processes to produce nanoscale materials and devices. *See* James E. Bailey, *Toward a Science of Metabolic Engineering*, 252 SCIENCE 1668 (1991); David H. Freedman, *Exploiting the Nanotechnology of Life*, 254 SCIENCE 1308 (1991); Paul W. Rothemund, *Folding DNA To Create Nanoscale Shapes and Patterns*, 440 NATURE 297 (2006).

14. *See* Peter Mostow, *Reassessing the Scope of Federal Biotechnology Oversight*, 10 PACE ENVTL. L. REV. 227, 240 (1992) ("Agencies must argue that biotechnology is not a radically new or different technology, and that biotechnology products are not dissimilar from products covered by existing regulatory mandates."); *id*. at 258 (contrasting the approach in Germany where courts rejected agency efforts to extend their existing statutory authority, which forced the national legislature to craft a comprehensive new approach designed with biotechnology in mind); *see also* Monique P. Nion, *Biotechnology and Environmental Law in Europe*, 34 JURIMETRICS J. 317 (1994) (elaborating on the German approach to regulating GMOs); *cf.* Peter Barton Hutt, *Research on Recombinant DNA Molecules: The Regulatory Issues*, 51 S. CAL. L. REV. 1435, 1444 (1978) (explaining, as part of a lengthy symposium issue dedicated to this emerging field, that federal agencies enjoyed ample regulatory authority under existing statutes to control commercial applications of biotechnology); Thomas O. McGarity & Karl O. Bayer, *Federal Regulation of Emerging Genetic Technologies*, 36 VAND. L. REV. 461, 537-40 (1983) (same, but also imagining circumstances under which specialized legislation might be desirable).

15. *See* Diane E. Hoffmann, *The Biotechnology Revolution and Its Regulatory Evolution*, 38 DRAKE L. REV. 471, 472-73 (1989); W. Wayne Withers, *Biotechnology: An Industry Perspective*, 34 U. KAN. L. REV. 665, 665 (1986); Holly Saigo, Note, *Agricultural Biotechnology and the Negotiation of the Biosafety Protocol*, 12 GEO. INT'L ENVTL. L. REV. 779, 783-84 n.27 (2000) (noting that biotech companies successfully lobbied the drafters of the Cartagena Biosafety Protocol to switch to the "living modified organism (LMO)" terminology so as to minimize the perceived differences between GM crops and conventional plant breeding); *see also* Vincent M. Brannigan, *Biotechnology: A First Order Technico-Legal Revolution*, 16 HOFSTRA L. REV. 545, 549 (1988) ("The problem has usually arisen when the legal system has not been able to easily classify a new technology in accordance with existing legal structures. The inability to apply existing doctrines creates a discontinuity in the law, and the interested parties try to take advantage of this discontinuity to secure a favorable legal verdict on the new technology."); *id*. at 549-50 ("The introduction of such a technology produces a period of conflict and confusion, as various parties attempt to control the new technology by making it fit preexisting legal structures."); Stuart M. Pape, *Regulation of New Technologies: Is Biotechnology Unique?*, 44 FOOD DRUG COSM. L.J. 173 (1989).

16. *See* 21 C.F.R. §§ 1271.10(a), 1271.20 (2006).

17. *See* Noah, *supra* note 11, at 1160.

context of nanotechnology.[18]

1. Early Responses to Biotech Breakthroughs

¶ 6 When recombinant DNA research first became possible, the scientific community recognized the potentially transformative nature of this breakthrough,[19] and it took the lead in trying to address some of the accompanying concerns. In 1975, after first announcing a voluntary moratorium,[20] a group of scientists meeting in Monterey, California developed consensus guidelines to govern experiments in genetic engineering.[21] One year later, the National Institutes of Health (NIH) issued guidelines for recombinant DNA research that it funded,[22] and other federal grant agencies, such as the National Science Foundation (NSF) – as well as private sponsors of such work – decided to follow these strictures.[23]

¶ 7 Although many scientists felt that such professional self-regulation and conditional grant funding would obviate the need for more direct federal oversight and

18. *See* Rick Weiss, *For Science, Nanotech Poses Big Unknowns*, WASH. POST, Feb. 1, 2004, at A1 (reporting that facilities manufacturing carbon nanotubes file "material safety data sheets" required by occupational health and safety regulations as if the material was identical to graphite even though such nanoparticles have different properties than the same substance in bulk form). "You can't simultaneously proclaim a product is new and has all these novel properties and at the same time claim that it can be regulated as if it were nothing different. . . . You can't have it both ways." *Id*. (quoting Eric Drexler, chairman of the Foresight Institute); *see also* Drexler & Wejnert, *supra* note 12, at 20 ("Existing regulations treat [nanoparticles] as particles of materials that are already well understood, failing to recognize that very fine particles have new biological and toxicological properties.").

19. *See* Maxine F. Singer, *Genetics and the Law: A Scientist's View*, 3 YALE L. & POL'Y REV. 315, 318 (1985) ("For a long time, biology was a descriptive science. Recently, with the advent of genetic engineering techniques, it has become a manipulative science – a technology, if you will. With this development, biology's potential for both good and evil has grown.").

20. *See* Paul Berg et al., *Potential Biohazards of Recombinant DNA Molecules*, 185 SCIENCE 303 (1974); Judith P. Swazey et al., *Risks and Benefits, Rights and Responsibilities: A History of the Recombinant DNA Research Controversy*, 51 S. CAL. L. REV. 1019, 1020-30 (1978).

21. *See* Paul Berg et al., *Asilomar Conference on Recombinant DNA Molecules*, 188 SCIENCE 991 (1975); *see also* Marcia Barinaga, *Asilomar Revisited: Lessons for Today?*, 287 SCIENCE 1584 (2000); Roger B. Dworkin, *Science, Society, and the Expert Town Meeting: Some Comments on Asilomar*, 51 S. CAL. L. REV. 1471 (1978) (offering an insider's critical account of this event).

22. *See* Guidelines for Research on Recombinant DNA Molecules, 41 Fed. Reg. 27,902 (1976). The agency liberalized its original guidelines, which had prevented most deliberate release experiments, just two years later. *See* Guidelines for Research on Recombinant DNA Molecules, 43 Fed. Reg. 60,101 (1978); *see also* Mack v. Califano, 447 F. Supp. 668 (D.D.C. 1978); *cf*. Found. on Econ. Trends v. Heckler, 756 F.2d 143, 153-55 (D.C. Cir. 1985) (enjoining deliberate release experiment of cold-tolerant GM food crops until the NIH conducted an environmental assessment). Since that time, the NIH has amended these guidelines on a regular basis. *See, e.g.*, Guidelines for Research Involving Recombinant DNA, 59 Fed. Reg. 34,496 (1994); *see also* Recombinant DNA Research: Proposed Actions Under Guidelines, 53 Fed. Reg. 12,752, 12,753 (1988) (noting that questions had arisen about coverage of the guidelines because of narrow initial definitions).

23. *See, e.g.*, Guidelines for Research Involving Recombinant DNA, 51 Fed. Reg. 16,598 (1986); Judith Areen, *Regulating Human Gene Therapy*, 88 W. VA. L. REV. 153, 157 (1985); *see also* Valerie M. Fogleman, *Regulating Science: An Evaluation of the Regulation of Biotechnology Research*, 17 ENVTL. L. 183 (1987).

regulation,[24] most observers felt uncomfortable with such an arrangement, especially once biotechnology work began to spread beyond the confines of academic labs.[25] Initially, a few localities responded to the relative lack of federal oversight by imposing restrictions on the research.[26] In 1980, in a testament to the speed with which research and development progressed in this field, the United States Supreme Court faced its first dispute concerning biotechnology, holding that a microorganism created through plasmid fusion, an older method of genetic engineering, qualified as patentable subject matter.[27]

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24. *See* John E. Barkstrom, *Recombinant DNA and the Regulation of Biotechnology: Reflections on the Asilomar Conference, Ten Years After*, 19 AKRON L. REV. 81, 103 (1985); Bernard D. Davis, *Bacterial Domestication: Underlying Assumptions*, 235 SCIENCE 1329, 1335 (1987); Clifford Grobstein, *Regulation and Basic Research: Implications of Recombinant DNA*, 51 S. CAL. L. REV. 1181, 1198 (1978) ("Scientists directly involved in this research necessarily feel threatened by the public debate and the possibility of external intervention."); Nicholas Wade, *Gene Splicing: Senate Bill Draws Charges of Lysenkoism*, 197 SCIENCE 348 (1987); Mark W. Lauroesch, Note, *Genetic Engineering: Innovation and Risk Minimization*, 57 GEO. WASH. L. REV. 100, 124, 130 n.177 (1988).

25. *See* Charles Weiner, *Is Self-Regulation Enough Today?: Evaluating the Recombinant DNA Controversy*, 9 HEALTH MATRIX 289 (1999) (providing a detailed account of this history, but questioning its overly technocratic focus); *id*. at 302 ("Despite the success in improving the safety of research, the quasi-self-regulation model developed in the recombinant DNA controversy is not adequate for expressing and enforcing societal and moral limits for potential genetic engineering applications such as human cloning or human germ-line interventions."); Richard Kevin Zepfel, Note, *Stopping a "Gruesome Parade of Horribles": Criminal Sanctions To Deter Corporate Misuse of Recombinant DNA Technology*, 59 S. CAL. L. REV. 641, 646-49 (1986) (recognizing that companies had a number of reasons for voluntarily complying with the NIH guidelines, but doubting that this would suffice); *cf.* Stuart Auchincloss, *Does Genetic Engineering Need Genetic Engineers?: Should the Regulation of Genetic Engineering Include a New Professional Discipline?*, 20 B.C. ENVTL. AFF. L. REV. 37, 57-63 (1993) (recommending that the federal government require that all deliberate releases of GMOs be subject to the supervision of newly licensed multidisciplinary scientists).

26. *See* David P. Rosenblatt, Comment, *The Regulation of Recombinant DNA Research: The Alternative of Local Control*, 10 B.C. ENVTL. AFF. L. REV. 37, 58 n.178, 66-77 (1982). It has moved beyond Berkeley and Cambridge. A few states have mandated compliance with the NIH guidelines or created separate permitting requirements for deliberate releases of GMOs. *See* MINN. STAT. § 18F.01-.13 (2004); MISS. CODE ANN. § 79-22-9 (2000); N.C. GEN. STAT. § 106-768 (2000); *see also* HAW. REV. STAT. § 321-11.6 (2002); 43 ILL. COMP. STAT. 95/0.01 (2000); ME. REV. STAT. ANN. tit. 7, §§ 231-236 (2001); OKLA. STAT. ANN. tit. 2, §§ 2011-2018 (2000); WIS. STAT. ANN. § 146.60 (2003); Hoffmann, *supra* note 15, at 537-39. Conversely, more than half a dozen states have acted to bar restrictions adopted by localities. *See* Gregory M. Lamb, *Super Foods Flex Their Clout: Unsuccessful at Federal Level, US Opponents Turn to States*, CHRISTIAN SCI. MONITOR, May 12, 2005, at 13.

27. *See* Diamond v. Chakrabarty, 447 U.S. 303 (1980); *see also* J.E.M. Ag. Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc., 534 U.S. 124 (2001) (holding that GM seeds are patentable); Rebecca S. Eisenberg, *Proprietary Rights and the Norms of Science in Biotechnology Research*, 97 YALE L.J. 177 (1987); John M. Golden, *Biotechnology, Technology Policy, and Patentability: Natural Products and Invention in the American System*, 50 EMORY L.J. 629 (1999). Although largely beyond the scope of this Article, questions of characterization may become centrally relevant in connection with intellectual property rights, a task for the U.S. Patent and Trademark Office (PTO). *See, e.g.*, 35 U.S.C. § 103(b) (2000); Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316, 1324-25 (Fed. Cir. 2002) (citing the PTO's written description guidelines applicable to biotech inventions); *see also* Dan L. Burk, *Biotechnology in the Federal Circuit: A Clockwork Lemon*, 46 ARIZ. L. REV. 441, 452-55 (2004); Linda J. Demaine & Aaron Xavier Fellmeth, *Reinventing the Double Helix: A Novel and Nonobvious Reconceptualization of the Biotechnology Patent*, 55 STAN. L. REV. 303 (2002); Alison E. Cantor, Note, *Using the Written Description and Enablement Requirements To Limit Biotechnology Patents*, 14 HARV. J.L. & TECH. 267, 282-83 (2000) ("Generally, patent law is not tailored to a specific technology, but in the field of biotechnology, there has been a noticeable trend toward using the enablement and written description requirements to limit the scope of patents." (footnote omitted)); *id*. at

¶ 8 One decade after the scientific community began to grapple with the potential consequences of this novel work, the federal government attempted to sketch out how it would approach the newly emerging field. In 1986, after convening an interagency working group, the White House Office of Science and Technology Policy (OSTP) issued a guideline entitled "The Coordinated Framework for Regulation of Biotechnology," which included separate policy statements from the different agencies that had participated and would have primary roles to play in its implementation: the United States Department of Agriculture (USDA), the Environmental Protection Agency (EPA), the FDA, the NIH, and the Occupational Safety and Health Administration (OSHA).[28] The guideline emphasized that, for the most part, the government would regulate the products rather than the processes of biotechnology, which the document denominated as "intergeneric organisms and pathogens."[29] In addition to this central precept, OSTP explained that it "sought to achieve a balance between regulation adequate to ensure health and environmental safety while maintaining sufficient regulatory flexibility to avoid impeding the growth of an infant industry."[30]

¶ 9 In essence, the executive branch decided that it would work to adapt existing rules as necessary but only to the extent that particular innovations represented fundamental departures from more conventional technologies: "The heart of that plan was to reinterpret existing laws, some of them passed decades earlier, to apply to the new technology. The result was a patchwork regulatory system that split jurisdiction among three agencies, all using different laws and standards."[31] A more detailed review

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307, 313 (speculating that courts may be taking into account bioethical concerns); Ruth E. Freeburg, Comment, *No Safe Harbor and No Experimental Use: Is It Time for Compulsory Licensing of Biotech Tools?*, 53 BUFF. L. REV. 351 (2005); William C. Mull, Note, *Using the Written Description Requirement To Limit Broad Patent Scope, Allow Competition, and Encourage Innovation in Biotechnology*, 14 HEALTH MATRIX 393, 405-35 (2004); Margaret Sampson, Comment, *The Evolution of the Enablement and Written Description Requirements Under 35 U.S.C. § 112 in the Area of Biotechnology*, 15 BERKELEY TECH. L.J. 1233, 1272-74 (2000).

28. *See* 51 Fed. Reg. 23,302 (1986); Establishment of the Biotechnology Science Coordinating Committee, 50 Fed. Reg. 47,174 (1985); Statement of Policy for Regulating Biotechnology Products, 49 Fed. Reg. 50,878 (1984); *see also* 42 U.S.C. § 6611 (2000) (establishing the OSTP).

29. *See* 51 Fed. Reg. at 23,306-07; *cf.* Principles for Federal Oversight of Biotechnology: Planned Introduction into the Environment of Organisms with Modified Hereditary Traits, 55 Fed. Reg. 31,118, 31,120 (1990) (proposing to broaden the definition to include all "organisms with deliberately modified hereditary traits"). For some of the initial academic responses to the Coordinated Framework, see Hoffmann, *supra* note 15, at 518-33; Gary E. Marchant, Note, *Modified Rules for Modified Bugs: Balancing Safety and Efficiency in the Regulation of Deliberate Release of Genetically Engineered Microorganisms*, 1 HARV. J.L. & TECH. 163 (1988); Robert Saperstein, Comment, *The Monkey's Paw: Regulating the Deliberate Environmental Release of Genetically Engineered Organisms*, 66 WASH. L. REV. 247 (1991); Michael P. Vandenbergh, Note, *The Rutabaga That Ate Pittsburgh: Federal Regulation of Free Release Biotechnology*, 72 VA. L. REV. 1529, 1541-67 (1986) (focusing on the EPA's role).

30. 51 Fed. Reg. at 23,302-03; *see also id.* at 23,303 ("Upon examination of the existing laws available for the regulation of products developed by traditional genetic manipulation techniques, the working group concluded that, for the most part, these laws as currently implemented would address regulatory needs adequately."); Mostow, *supra* note 14, at 268 n.159 ("Since its restrictive beginnings with the 1976 NIH Guidelines, the history of biotechnology regulation has been a history of steadily moving the burden of dispelling uncertainty onto potential regulators.").

31. Justin Gillis, *Biotech Regulation Falls Short, Report Says: Pew Study Calls for Better Oversight*, WASH. POST, Apr. 1, 2004, at E3. As it happens, one of the earliest federal product safety statutes, enacted

identified five federal agencies exercising regulatory jurisdiction under at least a dozen different statutes, most of which predated the advent of genetic engineering.[32] This frequent observation does not, however, distinguish biotechnology from other fields; rather, it mistakenly treats biotechnology as a monolithic enterprise when it makes more sense to appreciate its multiplicity.[33] In short, the multifaceted regulatory response to biotechnology reflects the potentially vast and varied reach of these innovative techniques. No doubt the products and processes of the petrochemical revolution (from plastics to pesticides) witnessed an equally fragmented exercise of regulatory authority. At least when it came to biotechnology, the executive branch recognized the need for some amount of coordination across agencies, even if it has not worked as well as hoped.[34]

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more than a century ago, focused on therapeutic products (i.e., vaccines) derived through biotechnology, at least as broadly defined. *See* Biologics Act, Pub. L. No. 57-244, 32 Stat. 328 (1902) (codified as amended at 42 U.S.C. § 262 (2000)); Gary E. Gamerman, *Regulation of Biologics Manufacturing: Questioning the Premise*, 49 FOOD & DRUG L.J. 213, 215-20 (1994); *id*. at 216 ("In this early stage of pharmaceutical biotechnology it was difficult, if not impossible, to identify what might be in a given package of vaccine or antitoxin, or whether it was contaminated by any pathogens.").

32. *See* Gregory N. Mandel, *Gaps, Inexperience, Inconsistencies, and Overlaps: Crisis in the Regulation of Genetically Modified Plants and Animals*, 45 WM. & MARY L. REV. 2167, 2228 (2004) ("[T]he regulations governing genetically modified products have been developed in a piecemeal, haphazard manner. Genetically modified plants and animals are now governed by as many as twelve different statutes and five different agencies or services."); *id*. at 2172 (explaining that the current regulatory system "is passive rather than proactive about risks, has difficulty adapting to biotechnology advances, and is highly fractured"); *id*. at 2173 ("[R]egulation of genetically modified products must be shifted from a haphazard model based on archaic statutes not intended to cover biotechnology to a regulatory system based on agency expertise in handling particular types of risks. This shift would remove from the current system numerous instances of regulatory overlap [and] inconsistency . . . ."); *id*. at 2230-46 (elaborating on these arguments); *see also* Gregory A. Jaffe, *Inadequacies in the Federal Regulation of Biotechnology*, 11 HARV. ENVTL. L. REV. 491, 528-32, 547 (1987); John Charles Kunich, *Mother Frankenstein, Doctor Nature, and the Environmental Law of Genetic Engineering*, 74 S. CAL. L. REV. 807, 823-46 (2001) (same); *id*. at 859-72 (offering a modest proposal that would consolidate authority in the EPA); Thomas O. McGarity, *Seeds of Distrust: Federal Regulation of Genetically Modified Plants*, 35 U. MICH. J.L. REFORM 403, 488 (2002) ("[T]he current regulatory regime was pieced together out of many different regulatory programs none of which envisioned the radical changes that modern biotechnology was capable of bringing about."); *id*. at 509 ("Unfortunately, the statutes that form the underlying foundation for the current federal regulatory regime were not enacted with biotechnology in mind and therefore leave several serious institutional and interpretational questions unresolved.").

33. *See* U.S. CONG., OFFICE OF TECHNOLOGY ASSESSMENT, BIOTECHNOLOGY IN A GLOBAL ECONOMY 31 (1991) (noting that there is no unitary "biotechnology industry"); Burk, *supra* note 27, at 451 ("[O]ne of the things that characterizes the biotechnology industry is that it is diverse and includes agricultural products, human pharmaceutical products, and a wide variety of other economic sectors. Some of these sectors are quite different from the others."); Thomas E. Lovejoy, *Bugs, Plants and Progress*, N.Y. TIMES, May 28, 1995, § 4, at 11; *cf*. U.S. DEP'T OF COMMERCE, U.S. INDUSTRIAL OUTLOOK 20-21 (1990) (explaining that, though biotechnology cuts across a number of sectors, firms using these techniques share common interests in questions concerning regulation and patent law).

34. *See* Administrative Conference of the U.S., Federal Regulation of Biotechnology (Recommendation No. 89-7), 54 Fed. Reg. 53,493 (1989) (calling, among other things, for greater interagency coordination); Sidney A. Shapiro, *Biotechnology and the Design of Regulation*, 17 ECOLOGY L.Q. 1, 18 & n.114, 26-36, 70 (1990) (same); *see also* Hoffmann, *supra* note 15, at 545-47 (identifying coordination problems under the 1986 framework); Jaffe, *supra* note 32, at 542 (same). Otherwise, agencies may vie with one another for primary jurisdiction. *See* Stephen Paul Mahinka & Kathleen M. Sanzo, *Biotechnology Litigation and Federal Regulation: Status and Implications*, 42 FOOD DRUG COSM.

¶ 10 Two decades after its publication, the Coordinated Framework remains in place, though many of the details have received extended attention in the intervening years. For instance, OSTP issued additional guidance in 1992 to address how different agencies should exercise their discretion in regulating environmental releases involving biotechnology.[35] This document, which reiterated previous concerns about imposing excessive regulatory burdens and the need to focus on the nature of the product rather than the underlying process, called for regulating only "unreasonable" risks, subjecting products to no greater restrictions than unmodified but otherwise similar products (a.k.a., a "substantial equivalence" test), and exempting classes of products likely to pose minimal risks.[36] Ten years later, OSTP called on the three primary regulatory agencies to update their policies to reflect the inevitability of contamination by GM crops.[37]

¶ 11 In addition, each participating agency has, to a greater or lesser extent, continued adapting its particular policies.[38] For instance, in the waning days of the Clinton administration, the FDA issued a package of proposals that generally would have increased the rigor of its regulatory approach to a range of different biotechnology products,[39] but these efforts stalled with the transition to the Bush administration.[40]

L.J. 500, 514-15 (1987). Moreover, some amount of competition and disagreement among agencies may have a silver lining in promoting dynamic tension and creativity. *Cf*. Michael C. Dorf & Charles F. Sabel, *A Constitution of Democratic Experimentalism*, 98 COLUM. L. REV. 267, 315 (1998) ("A central lesson of the limitations of New Deal institutions is that effective government services and regulations must be continuously adapted and recombined to respond to diverse and changing local conditions . . . .").

35. *See* Exercise of Federal Oversight Within Scope of Authority: Planned Introduction of Biotechnology Products into the Environment, 57 Fed. Reg. 6753 (1992).

36. *See id*. at 6756-57. The notice dropped an earlier proposal that had listed exempt categories. *See* Principles for Federal Oversight of Biotechnology: Planned Introduction into the Environment of Organisms with Modified Hereditary Traits, 55 Fed. Reg. 31,118, 31,121 (1990). For a detailed criticism of this announcement, see Mostow, *supra* note 14, at 237-64. For broader critiques of the use of the substantial equivalence standard at the core of this regulatory approach, see McGarity, *supra* note 32, at 426-32; *id*. at 405 ("With strong encouragement from the White House, the two federal agencies with primary regulatory jurisdiction over GM foods . . . have relied upon a controversial regulatory principle called 'substantial equivalence' as the primary vehicle for assessing and managing the risks that GM foods pose to human health."); *id*. at 431 ("[T]he substantial equivalence doctrine is the bedrock principle underlying the current regulatory regime for biotechnology in the United States."); *id*. at 489-90 (describing waning support for this doctrine); Erik Millstone et al., *Beyond "Substantial Equivalence*," 401 NATURE 525 (1999).

37. *See* Proposed Federal Actions To Update Field Test Requirements for Biotechnology Derived Plants and To Establish Early Food Safety Assessments for New Proteins Produced by Such Plants, 67 Fed. Reg. 50,578 (2002); *see also* Andrew Pollack, *Earlier Safety Reviews Proposed for Gene-Altered Crops*, N.Y. TIMES, Aug. 2, 2002, at C3; Jonathan D. Rockoff, *Bioengineering Guides Issued: FDA Asks Companies To Vouch for Genetically Modified Plants' Safety*, BALT. SUN, June 22, 2006, at 4A.

38. *See* Judith E. Beach, *No "Killer Tomatoes": Easing Federal Regulation of Genetically Engineered Plants*, 53 FOOD & DRUG L.J. 181 (1998); Emily Marden, *Risk and Regulation: U.S. Regulatory Policy on Genetically Modified Food and Agriculture*, 44 B.C. L. REV. 733, 784-86 (2003) (summarizing the trajectory of this evolution in relationship to GM crops); *id*. at 745-84 (detailing these developments). *See generally* United States Regulatory Agencies Unified Biotechnology Website, http://usbiotechreg.nbii.gov (last visited July 14, 2006).

39. *See* Marc Kaufman, *FDA Issues Biotech Food Rules: Proposals Address Labeling, Advance Notice of New Products*, WASH. POST, Jan. 18, 2001, at E3; Andrew Pollack, *F.D.A. Plans New Scrutiny in Areas of Biotechnology*, N.Y. TIMES, Jan. 18, 2001, at A12; *see also* FDA Ctr. for Food Safety & Applied

Although Part II of this Article focuses on the FDA's role, the EPA, which extended its pesticide jurisdiction to assert regulatory authority over plants engineered for enhanced resistance to pests,[41] also has remained active in trying to update its policies,[42] and the Animal and Plant Health Inspection Service (APHIS), a unit of USDA, plays a supervisory role for other agricultural applications of biotechnology.[43]

2. Common Gripes About Incrementalism

¶ 12 Disagreements persist about the wisdom and success of this incremental

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Nutrition (CFSAN), *Biotechnology*, http://www.cfsan.fda.gov/~lrd/biotechm.html (last visited July 14, 2006). The proposals are discussed more fully where relevant in the sections that follow.

40. *See infra* note 157 and accompanying text. The party that controlled the White House undoubtedly has shaped the character of the federal government's response to biotechnology, most notably reflected in the Coordinated Framework issued during President Reagan's second term. *See* Wilson Huhn, *Three Legal Frameworks for Regulating Genetic Technology*, 19 J. CONTEMP. HEALTH L. & POL'Y 1, 29 (2002) ("During the Reagan administration, the executive branch made three fateful decisions that weakened administrative regulation of genetic technology."); McGarity, *supra* note 32, at 431 (noting that OSTP's 1986 Coordinated Framework was "devised by an Administration that was very reluctant to impose regulatory restrictions on a rapidly developing new industry"); *cf.* Lars Noah, *A Miscarriage in the Drug Approval Process?: Mifepristone Embroils the FDA in Abortion Politics*, 36 WAKE FOREST L. REV. 571, 572-74 & n.8 (2001) (making a similar point in connection with RU-486).

41. *See* Statement of Policy: Microbial Products Subject to the Federal Insecticide, Fungicide, and Rodenticide Act and the Toxic Substances Control Act, 51 Fed. Reg. 23,313 (1986); *see also* Plant Pesticides Subject to the Federal Insecticide, Fungicide and Rodenticide Act, 59 Fed. Reg. 60,519 (1994); Microbial Pesticides; Experimental Use Permits and Notifications, 59 Fed. Reg. 45,600 (1994). The Toxic Substances Control Act (TSCA), 15 U.S.C. §§ 2601-2629 (2000), also gives the EPA some authority over a broader range of biotechnology products. *See* 40 C.F.R. pt. 725 (2005); *see also* Robin A. Chadwick, Note, *Regulating Genetically Engineered Microorganisms Under the Toxic Substances Control Act*, 24 HOFSTRA L. REV. 223 (1995).

42. *See, e.g.*, Regulations Under the Federal Insecticide, Fungicide and Rodenticide Act for Plant-Incorporated Protectants (Formerly Plant-Pesticides), 66 Fed. Reg. 37,772 (2001) (to be codified at 40 C.F.R. pts. 152, 174); Exemption from the Requirement for a Tolerance Under the Federal Food, Drug, and Cosmetic Act for Residues of Nucleic Acids That Are Part of Plant-Incorporated Protectants (Formerly Plant-Pesticides), 66 Fed. Reg. 37,817 (2001) (codified at 40 C.F.R. § 174.475 (2005)); Exemption from the Requirement for a Tolerance Under the Federal Food, Drug, and Cosmetic Act for Residues Derived Through Conventional Breeding from Sexually Compatible Plants of Plant-Incorporated Protectants (Formerly Plant-Pesticides), 66 Fed. Reg. 37,830 (2001) (to be codified at 40 C.F.R. pt. 174); Plant-Incorporated Protectants (Formerly Plant-Pesticides), Supplemental Proposal, 66 Fed. Reg. 37,855 (2001).

43. Under the Plant Protection Act, 7 U.S.C. §§ 7701-7772 (2000), which covers all crops other than pest-protected plants subject to the EPA's jurisdiction under FIFRA, *see* Plant Pest Regulations: Update of Current Provisions, 66 Fed. Reg. 51,340 (2001), the USDA exercises regulatory supervision over agricultural biotechnology. APHIS implements these requirements under its "Biotechnology Permitting Program," which has inherent flexibility in allowing the agency to impose a variety of conditions as it deems necessary (primarily to ensure containment), though one decade ago the agency had reduced some of these regulatory burdens. *See* Genetically Engineered Organisms and Products: Simplification of Requirements and Procedures for Genetically Engineered Organisms, 62 Fed. Reg. 19,903 (1997); Genetically Engineered Organisms and Products: Simplification of Requirements and Procedures for Genetically Engineered Organisms, 60 Fed. Reg. 43,567 (1995) (codified at 7 C.F.R. pt. 340 (2006)); *see also* Kevin Bastian, Comment, *Biotechnology and the United States Department of Agriculture: Problems of Regulation in a Promotional Agency*, 17 ECOLOGY L.Q. 413, 438-45 (1990) (concluding that the agency "is biased in favor of biotechnology"); Jill Carroll, *Reviews of Crops Altered by Genetics Are "Superficial,"* WALL ST. J., Feb. 21, 2002, at B6.

regulatory approach.[44] The European Union (EU) has taken a decidedly different tack from the United States, focusing on the process rather than the end products and adopting restrictions specifically geared toward biotechnology.[45] As one commentator explained:

> In its cruder forms, biotechnology has been used to produce beer, wine, and cheeses, as well as to selectively breed plants and livestock. Genetic engineering can thus be viewed either as a step in the long evolution of biotechnology or a radical break, or revolution, in that process. The tension between these two perspectives accounts for much of the controversy surrounding the regulation of biotechnology.[46]

¶ 13 This Article will review some of the recent technological challenges and regulatory responses in an effort to gauge such assessments. At a more fundamental level, a number of commentators have emphasized the distinctiveness of biotechnology and the consequent need for appropriately tailored responses by legal institutions.[47] This Article seeks to test that broad proposition, offering a decidedly contrarian take on the subject.

¶ 14 Critics often point out that, at least in the case of many GM crops, sellers need to generate little or no safety information,[48] but this does not differentiate biotech foods

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44. *See* Hoffmann, *supra* note 15, at 539-43; Julie Teel, *Regulating Genetically Modified Products and Processes: An Overview of Approaches*, 8 N.Y.U. ENVTL. L.J. 649 (2000); William Allen, Note, *The Current Federal Regulatory Framework for Release of Genetically Altered Organisms into the Environment*, 42 FLA. L. REV. 531 (1990).

45. *See* Helen Lawton Smith, *Regulating Science and Technology: The Case of the UK Biotechnology Industry*, 27 LAW & POL'Y 189, 197 (2005) ("The EU's approach to regulation is significantly different from that of the U.S. European Union countries . . . have enacted process-driven legislation to regulate GMOs, whereas in the U.S., regulation is driven by the intended use of the product . . . . Moreover, unlike the U.S., instead of relying on existing regulation, the EU has enacted new regulation for GMOs."); *id*. at 204-05 (explaining that the UK's original regulatory approach had more in common with that of the United States); *id*. at 210 (concluding "that the UK is affected by the emerging politics of regulation within Europe – which appear to be creating an unfavorable regulatory climate for the biotech production system as a whole"); *id*. at 193 (recounting "that in 2002 worldwide there were 4,362 biotech companies, of which half were in the U.S., . . . but only 102 were in Europe"); *see also* Filippa Corneliussen, *The Impact of Regulations on Firms: A Case Study of the Biotech Industry*, 27 LAW & POL'Y 429 (2005).

46. Mostow, *supra* note 14, at 229.

47. *See, e.g.*, Dan L. Burk, *Introduction: A Biotechnology Primer*, 55 U. PITT. L. REV. 611, 632 (1994) (concluding "that both the technology itself and the industry it has generated have unique characteristics that will shape the legal solutions to the societal questions that biotechnology poses"); Mandel, *supra* note 32, at 2258 ("It is not surprising that, in an area developing as rapidly as biotechnology, a regulatory structure proposed two decades ago and based on a patchwork of statutes and regulatory processes created even earlier, would prove fundamentally flawed and unable to adapt to current developments."). For more skeptical assessments of this frequent claim, see Brannigan, *supra* note 15, at 546, 552, 568 (conceding the revolutionary nature of genetic engineering, but criticizing the search for superficial analogies); Michael H. Shapiro, *Is Bioethics Broke?: On the Idea of Ethics and Law "Catching Up" with Technology*, 33 IND. L. REV. 17, 152-62 (1999).

48. *See, e.g.*, McGarity, *supra* note 32, at 479-81; *id*. at 424 (" [S]ubstantial uncertainties permeate the existing state of knowledge regarding the risks and benefits posed by GM foods. Agricultural biotechnology companies have undertaken very little testing of whole GM foods and of novel proteins and other products expressed in GM foods."); *id*. at 444 ("This wholesale delegation to the manufacturer of the safety assessment process seems inconsistent with the regulatory regime established by Congress for food

from many other food-use substances.[49] The same might be said about objections to a largely self-regulatory approach.[50] In addition, the previously mentioned "patchwork" arrangement that has received frequent criticism existed before the advent of biotechnology,[51] though the shortcomings of such a division of responsibility may have become starker once faced with these novel products and processes.

¶ 15 One author pointed out, among other things, that the EPA deals with food safety issues arising from GM plants producing their own protection against pests while the FDA deals with food safety issues from all other types of GM plants,[52] and he also complained that certain regulations governing biotechnology products depend entirely on the seller's intended use.[53] Neither one of these points is in any sense unique to GMOs. For instance, the FDA's jurisdiction to regulate different categories of products turns largely on their intended use.[54] Although perhaps incoherent and indefensible, these do not represent flaws peculiar to the federal oversight of the fruits of biotechnology. Even the repeated suggestion that the United States has decided to focus on products rather than processes does not stand up to close scrutiny insofar as some regulatory agencies

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additives."); *see also id*. at 431 ("Because it is based in large part on a policy determination that agencies and companies should not have to waste resources on unnecessary testing and evaluation, the substantial equivalence doctrine is not so much a 'scientific' risk assessment tool as it is an excuse for regulatory agencies to avoid their responsibilities."); *id*. at 493, 497-99 (urging resort to the "precautionary principle" for this reason).

49. *See* Lars Noah & Richard A. Merrill, *Starting from Scratch?: Reinventing the Food Additive Approval Process*, 78 B.U. L. REV. 329, 333-36 (1998) (summarizing the basic food adulteration provisions); *id*. at 341-42 (delineating the range of food use substances that remain subject to the basic adulteration provisions because Congress failed to included them in the definition of "food additive"); *id*. at 375-76, 438 (noting that free-riding undermines the incentives to generate the safety data necessary for filing a food additive petition); *id*. at 383-85 (explaining that "interim food additives" remain in "limbo").

50. *See* Lars Noah, *Assisted Reproductive Technologies and the Pitfalls of Unregulated Biomedical Innovation*, 55 FLA. L. REV. 603, 624-33, 648 (2003) (concluding that self-regulation has not worked well in the fertility industry).

51. *See* Richard A. Merrill & Jeffrey K. Francer, *Organizing Federal Food Safety Regulation*, 31 SETON HALL L. REV. 61, 115-25 (2000); *id*. at 66 ("In the last fifty years, more than a dozen expert panels inside and outside government have called for the consolidation of the federal agencies that exercise and share food safety responsibility."); *see also id*. at 77 ("The controversy over [GM] foods . . . provides a window on the fragmented nature of food safety regulation in the United States."); Cindy Skrzycki, *Food-Safety Agencies Mince Their Meats*, WASH. POST, Nov. 22, 2005, at D1 (reporting that, apart from the FDA and USDA, "[a]bout 10 more agencies have some food-safety responsibility under some 35 statutes"). Such patchwork arrangements arise in other regulatory arenas as well and attract similar objections. *See, e.g.*, Lars Noah, *Challenges in the Federal Regulation of Pain Management Technologies*, 31 J.L. MED. & ETHICS 55, 60 (2003) (criticizing the division of responsibility between the FDA and the Drug Enforcement Administration with respect to controlled substances).

52. *See* Mandel, *supra* note 32, at 2223, 2240-41 ("There is no scientific rationale for this distinction. It is the result of the historical accident of transgenic pest-protected plants falling within FIFRA's statutory language."); *see also id*. at 2231-33 (arguing that only the EPA has the necessary expertise to address environmental risks associated with biotechnology); *id*. at 2249 (recommending that the FDA take responsibility for evaluating risks to human health).

53. *See id*. at 2235 ("Thus, the EPA does not regulate a transgenic corn variety modified to produce a known pesticide because the developer is developing the corn for purposes other than pest resistance . . . .").

54. *See* Noah & Merrill, *supra* note 49, at 342 ("The FDA routinely grapples with questions about the intended use of an article to determine its appropriate regulatory classification as, for instance, a food, drug, medical device, or cosmetic.").

have paid closer attention to the inputs leading to end-products. In ensuring the safety of both conventional and GM foods, for example, both the FDA and the USDA have become more attentive to policing compliance with good manufacturing practices (GMPs) rather than inspecting finished products.[55]

¶ 16 Finally, complaints about the use of the substantial equivalence test as a guiding principle for calibrating the level of risk regulation fail to appreciate both the prevalence of this approach in other regulatory arenas and its practical advantages. For instance, risk assessment for new chemicals may begin with a search for "structure activity relationships," which refer to the degree of similarity to known toxic agents.[56] In setting priorities for the use of scarce agency resources, substantial equivalence provides an admittedly imprecise shorthand method for targeting those substances of highest concern.[57] In addition, this test avoids the common mistake of subjecting newer

55. *See, e.g.*, FDA, Hazard Analysis and Critical Control Point (HACCP): Procedures for the Safe and Sanitary Processing and Importation of Juice, 66 Fed. Reg. 6138 (2001); USDA, Pathogen Reduction: Hazard Analysis and Critical Control Point (HACCP) Systems, 61 Fed. Reg. 38,806 (1996) (codified in scattered sections of 9 C.F.R.); Todd S. Purdum, *Meat Inspections Facing Overhaul, First in 90 Years*, N.Y. TIMES, July 7, 1996, § 1, at 1; *see also* FDA, Notice of Public Meeting, Animal Feed Safety System: A Comprehensive Risk-Based Safety Program for the Manufacture and Distribution of Animal Feeds, 70 Fed. Reg. 6448 (2005) (expressing interest in extending HACCP to the regulation of animal feed); Edward L. Korwek, *FDA Regulation of Biotechnology as a New Method of Manufacture*, 37 FOOD DRUG COSM. L.J. 289 (1982); Edward L. Korwek, *The NIH Guidelines for Recombinant DNA Research and the Authority of FDA To Require Compliance with the Guidelines*, 21 JURIMETRICS J. 264, 271 (1981) (arguing that the FDA could use its GMP rules to regulate biotechnology products); *cf.* Douglas A. Kysar, *Preferences for Processes: The Process-Product Distinction and the Regulation of Consumer Choice*, 118 HARV. L. REV. 526 (2004).

56. *See, e.g.*, 21 C.F.R. § 312.42(a)(2) (2006) (Phase I studies of investigational new drugs); EPA, Proposed Guidelines for Carcinogen Risk Assessment, 61 Fed. Reg. 17,960, 17,977-78 (1996); Tozzi v. HHS, 271 F.3d 301, 305 (D.C. Cir. 2001) (quoting the National Toxicology Program's 1996 criteria for listing a substance as "reasonably anticipated to be a human carcinogen," which include evidence that "the agent belongs to a well defined structurally-related class of substances whose members are listed" as suspected carcinogens); NATIONAL RESEARCH COUNCIL, RISK ASSESSMENT IN THE FEDERAL GOVERNMENT: MANAGING THE PROCESS 20-23 (1983); Bernard D. Goldstein & Mary Sue Henifin, *Reference Guide on Toxicology*, *in* FED. JUD. CTR., REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 421 (2d ed. 2000); Erica Beecher-Monas, *The Heuristics of Intellectual Due Process: A Primer for Triers of Science* 75 N.Y.U. L. REV. 1563, 1623-24 (2000); David Roe, *Ready or Not: The Coming Wave of Toxic Chemicals*, 29 ECOLOGY L.Q. 623, 629 n.18 (2002). Of course, as demonstrated once again by recent studies involving acrylamide (a by-product of frying certain foods) and phthalates (widely used plasticizers), hazards to human health often become apparent only after the fact. *See* Dawn Fallik, *Chemical Heads: Those Unpronounceable Ingredients in Hair-Care Products Raise Eyebrows About the Effects on Users and the Environment*, PHILA. INQUIRER, Oct. 4, 2004, at E1; Sara Solovitch, *One Chemical, Many Foods*, L.A. TIMES, Dec. 19, 2005, at F1; *see also* Valerie J. Watnick, *Our Toxics Regulatory System and Why Risk Assessment Does Not Work: Endocrine Disrupting Chemicals as a Case in Point*, 2004 UTAH L. REV. 1305; *GAO Urges Stronger Law on Toxic Substances*, WASH. POST, July 14, 2005, at A10 (reporting that "chemical companies have provided the EPA with health data for only about 15 percent of the chemical compounds that have been introduced over the past 30 years," and that "the EPA has sought information about health dangers for fewer than 200 of the tens of thousands of industrial compounds in use since before the late 1970s").

57. *See* David L. Devernoe, Note, *Substantial Equivalence: A Valid International Sanitary and Phytosanitary Risk Assessment Objective for Genetically Modified Foods*, 51 CASE W. RES. L. REV. 257, 288-93 (2000); *see also* John S. Applegate, *Worst Things First: Risk, Information and Regulatory Structure in Toxic Substances Control*, 9 YALE J. ON REG. 277 (1992).

technologies to greater regulatory burdens than the older and often riskier technologies for which they would substitute.[58] Labeling this better-safe-than-sorry approach for regulating novel products as the "precautionary principle" does not alter the fact that it privileges existing sources of sometimes well-known risks and discourages innovations that may, on the whole, provide greater safety.[59] If nothing else, norms of fairness in administrative procedure require treating like products alike.[60]

B. The First Wave

¶ 17 Over the course of the last decade, biotechnology has entered the marketplace, offering innovative therapeutic and agricultural products to consumers. As the federal regulatory agency with primary jurisdiction over these two broad classes of products, the Food and Drug Administration has encountered a sometimes steep but not insurmountable learning curve. As explained in the sections that follow, the FDA's

58. *See* Peter Huber, *The Old-New Division in Risk Regulation*, 69 VA. L. REV. 1025, 1073-75, 1078-79, 1093-95 (1983); *id*. at 1105 ("[C]omparative regulation of different sources of risk within the same risk market is necessary to bridge the gap between old and new risks. Regulation should not exclude new substitutes if they would replace more hazardous old products."); *see also id*. at 1028 ("Whether the reasons are political or economic, there is a manifest congressional and agency perception that improving the risk environment by excluding new risks is cheaper than improving it by attacking old ones."); *id*. ("[T]he [old-new risk] division promotes regulatory decisions that are technologically regressive, . . . [and it] incorporates a bias against new technology. This bias may impede desirable risk-reducing technological transformations."); *id*. at 1041-42; *id*. at 1053 ("A claim that new risks are intrinsically more serious than old ones has no empirical foundation."); *id*. at 1066 ("[A] system of regulation that divides the world into old and new risks may overlook the social costs of establishing a systematic bias in favor of old technology. By indulging old sources of risk while guarding against new ones more stringently, risk regulation divided along old-new lines creates a clear danger of hampering technological innovation."); Peter Huber, *Safety and the Second Best: The Hazards of Public Risk Management in the Courts*, 85 COLUM. L. REV. 277, 309-14, 329, 335 (1985) (explaining that the judiciary is particularly likely to make regressive risk choices).

59. *See* Frank B. Cross, *Paradoxical Perils of the Precautionary Principle*, 53 WASH. & LEE L. REV. 851, 859-914 (1996) (identifying several perverse consequences that flow from allegiance to this principle); Cass R. Sunstein, *Beyond the Precautionary Principle*, 151 U. PA. L. REV. 1003, 1054-55 (2003) ("The precautionary principle appears to offer guidance only because people blind themselves to certain aspects of the risk situation, focusing on a mere subset of the hazards that are at stake."); *id*. at 1038-41 (discussing the "mythical benevolence of nature"); *id*. at 1021, 1037 (making brief references to GM foods for purposes of illustration); Stephen F. Williams, *Squaring the Vicious Circle*, 53 ADMIN. L. REV. 257, 268 (2001) ("There are a variety of formulations of this principle, all loosely purporting to be applications of a bunch of appealing adages: 'better safe than sorry,' 'an ounce of prevention is worth a pound of cure,' or 'look before you leap.'"); *id*. ("[T]he adage that it's better to be safe than sorry assumes that the speaker will pursue safety only up to a reasonable point, not that he'll become paranoid and refuse to get out of bed."); *id*. at 269 (discussing flaws in applying the principle to GM foods). *But see* Applegate, *supra* note 7, at 249-55 (offering a fairly nuanced account of this approach, and concluding that "GMOs are a good candidate for the application of the precautionary principle").

60. Thus, courts have chastised the FDA when it acts inconsistently in regulating similarly-situated products. *See* United States v. Diapulse Corp. of Am., 748 F.2d 56, 61-62 (2d Cir. 1984); Rhodia, Inc. v. FDA, 608 F.2d 1376, 1379 (D.C. Cir. 1979); Nat'l Nutritional Foods Ass'n v. Mathews, 557 F.2d 325, 337 (2d Cir. 1977); Bracco Diagnostics, Inc. v. Shalala, 963 F. Supp. 20, 28 (D.D.C. 1997); United States v. Undetermined Quantities . . . Exachol, 716 F. Supp. 787, 795 (S.D.N.Y. 1989). *But cf.* United States v. Sage Pharm., Inc., 210 F.3d 475, 480 (5th Cir. 2000) (holding that the FDA could target one firm for selling unapproved new drugs even though it had not yet acted against others who distributed substantially similar products).

policies have evolved alongside the growing commercialization of the biotech industr(ies).

1. Therapeutic Breakthroughs and "Orphan" Drugs

¶ 18 Traditionally, the pharmaceutical industry focused on small molecule drugs. Biotechnology offered a pair of advances: a new method for synthesizing such drugs and techniques for producing protein-based and other large molecule drugs.[61] A third application, which deviates even more profoundly from the conventional drug model, would correct certain diseases at their source by introducing bioengineered viruses into a patient's cells as a way of overwriting some genetic defect, but, after fifteen years of clinical trials, "gene therapy" has not yet lived up to expectations – it has not worked for most genetic diseases (e.g., cystic fibrosis),[62] and, in the one rare condition that it apparently has succeeded in curing (i.e., X-linked severe combined immunodeficiency), the technique triggered leukemia.[63] Although scientists remain hopeful that switching to different viruses to use as vectors will avoid such side effects in the future, the FDA has once again put an indefinite hold on this research.[64]

¶ 19 Taking gene therapy one speculative step further, some commentators fear that the final frontier of biotechnology will usher in genetically modified human beings.[65] Stem cell research, which simply creates cell lines from blastocysts, represents the latest craze in biomedicine, but it does not seem to fit within the narrow definition of biotechnology, and even eventual therapeutic applications would seem little different from organ transplants between different people.[66] Preimplantation genetic diagnosis,

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61. *See* Ann Gibbons, *Biotech's Second Generation*, 256 SCIENCE 766 (1992).

62. *See* Jerry E. Bishop, *Biotechnology: . . . but Trials Deflate Hope for Therapies*, WALL ST. J., Sept. 28, 1995, at B1.

63. *See* Rick Weiss, *Dream Unmet 50 Years After DNA Milestone: Gene Therapy Debacle Casts Pall on Field*, WASH. POST, Feb. 28, 2003, at A1. Scientists recently reported early success with a far more precise method for treating genetic diseases. *See* Rick Weiss, *Technique To Fix DNA Flaws Is Tested*, WASH. POST, Apr. 4, 2005, at A2. Researchers also have developed a related therapeutic technique that harnesses genetically modified viruses and other infectious agents with an affinity for cancer cells to target and destroy solid tumors. *See* Alice Park, *When Bad Bugs Go Good*, TIME, Mar. 28, 2005, at 52.

64. *See* Rick Weiss, *Boy's Cancer Prompts FDA To Halt Gene Therapy*, WASH. POST, Mar. 4, 2005, at A2. *See generally* NIH, Recombinant DNA Research: Actions Under the Guidelines, 62 Fed. Reg. 59,032 (1997) (transferring review authority to the FDA); FDA, Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products, 58 Fed. Reg. 53,248 (1993); David A. Kessler et al., *Regulation of Somatic-Cell Therapy and Gene Therapy by the Food and Drug Administration*, 329 NEW ENG. J. MED. 1169 (1993); Joseph M. Rainsbury, *Biotechnology on the RAC – FDA/NIH Regulation of Human Gene Therapy*, 55 FOOD & DRUG L.J. 575 (2000); Wilder J. Leavitt, Comment, *Regulating Human Gene Therapy: Legislative Overreaction to Human Subject Protection Failures*, 53 ADMIN. L. REV. 315 (2001).

65. *See* Joel Garreau, *Inventing Our Evolution: We're Almost Able To Build Better Human Beings, but Are We Ready?*, WASH. POST, May 16, 2005, at A1.

66. *Cf.* Rick Weiss, *Contentious Hearing Focuses on Stem Cells*, WASH. POST, July 13, 2005, at A19 (discussing suggestions to develop "embryos that might not pass muster as 'human' because they have been engineered to lack a gene crucial for development into a baby"); Rick Weiss, *Skin Cells Converted to Stem Cells*, WASH. POST, Aug. 22, 2005, at A1 (reporting that researchers had fused embryonic stem cells with somatic cells but still needed to find a way of removing the additional genetic material from the resulting hybrid cells). Somatic cell nuclear transfer (SCNT), which has been suggested as a method of

which uses amplification techniques to read the genome of an in vitro fertilized embryo before transfer into the uterus, arguably facilitates a form of population-wide engineering even if it does not alter the genetic characteristics of the particular embryo.[67] Germ-line therapies would, however, involve fundamental alterations in a human being and his or her progeny. Once they become feasible, these techniques will raise a host of serious legal and ethical questions.[68]

¶ 20 In the meantime, after something of a slow start, biotechnology has begun to deliver the goods in the pharmaceutical field.[69] The ever growing list of FDA-approved biotech drugs (now numbering more than 150) includes the following products: insulin (Eli Lilly's Humulin®) for diabetes,[70] human growth hormone (hGH) (Eli Lilly's

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avoiding the risks of rejection, would represent a form of genetic engineering insofar as the nuclear material of a fertilized egg would get swapped with the material of another individual (though not entirely insofar as mitochondrial DNA remains). The first reported success of therapeutic cloning with human embryos proved to be a hoax, *see* Rick Weiss, *Stem Cell Advance Is Fully Refuted: Investigator Says Korean's Colonies Do Not Exist*, WASH. POST, Dec. 30, 2005, at A1, but other researchers continue to try it, *see* Carl T. Hall, *UCSF Resumes Human Embryo Stem Cell Work: Scientists Hope To Generate Lines by Cloning Donated Eggs*, S.F. CHRON., May 6, 2006, at A1. Even without SCNT, some of the processes suggested for triggering differentiation by stem cells might qualify broadly as genetic engineering even if not a form of recombinant DNA.

67. *See* Michael J. Malinowski, *Choosing the Genetic Makeup of Children: Our Eugenics Past, Present, and Future?*, 36 CONN. L. REV. 125 (2003); Vicki G. Norton, Comment, *Unnatural Selection: Nontherapeutic Preimplantation Genetic Screening and Proposed Regulation*, 41 UCLA L. REV. 1581 (1994); Note, *Regulating Preimplantation Genetic Diagnosis: The Pathologization Problem*, 118 HARV. L. REV. 2770 (2005).

68. *See* Maxwell J. Mehlman, *The Law of Above Averages: Leveling the New Genetic Enhancement Playing Field*, 85 IOWA L. REV. 517 (2000); Michael J. Reiss, *What Sort of People Do We Want? The Ethics of Changing People Through Genetic Engineering*, 13 NOTRE DAME J.L. ETHICS & PUB. POL'Y 63 (1999); Michael H. Shapiro, *Fragmenting and Reassembling the World: Of Flying Squirrels, Augmented Persons, and Other Monsters*, 51 OHIO ST. L.J. 331 (1990); Michael H. Shapiro, *The Technology of Perfection: Performance Enhancement and the Control of Attributes*, 65 S. CAL. L. REV. 11 (1991); Sarah M. Markwood, Comment, *Creating a Perfect Human Is Not So Perfect: The Case for Restricting Genetic Enhancement Research*, 110 PENN ST. L. REV. 473 (2005); Symposium, *Genetic Technology: Social Values and Personal Autonomy in the 21st Century*, 34 WAKE FOREST L. REV. 557 (1999); Symposium, *Manufactured Humanity: The Ethics and Legality of Stem Cell Research, Bioengineering, and Human Cloning*, 65 ALB. L. REV. 587 (2002); *see also* Christine Willgoos, Note, *FDA Regulation: An Answer to the Questions of Human Cloning and Germline Gene Therapy*, 27 AM. J.L. & MED. 101 (2001).

69. *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, 211-12, 250-52 (1996); Andrew Pollack, *Signs That Biotech Has a Healthier Future*, N.Y. TIMES, Apr. 4, 2006, at C4 ("In 2005, for the third consecutive year, new biotechnology drugs received more approvals from the [FDA] than drugs from big pharmaceutical companies [18 vs. 11]."). *See generally* RONALD A. RADER, BIOPHARMACEUTICAL PRODUCTS IN THE U.S. AND EUROPEAN MARKETS (4th ed. 2005). An early summary of FDA approvals of biotech drugs listed just five products. *See* Jane M. Marciniszyn, *What Has Happened Since* Chakrabarty*?*, 2 J.L. & HEALTH 141, 150-56 (1988). By 1995, that had increased to 32 products. *See FDA Is Eliminating Special Restrictions on Biotechnology Drugs*, N.Y. TIMES, Nov. 10, 1995, at D8.

70. *See* Irving S. Johnson, *Human Insulin from Recombinant DNA Technology*, 219 SCIENCE 632, 634-35 (1983); Cristine Russell, *FDA Approves Insulin Made by Splicing Genes*, WASH. POST, Oct. 30, 1982, at A6.

Humatrope® and Genentech's Nutropin®) for short stature,[71] erythropoietin (EPO) (Johnson & Johnson's Procrit® and Amgen's Epogen®) for anemia (particularly in patients receiving kidney dialysis),[72] tissue plasminogen activator (tPA) (Genentech's Activase® (alteplase)) for heart attack and stroke, granulocyte-colony stimulating factor (G-CSF) (Amgen's Neupogen® (filgrastim)) for infections after chemotherapy, interferon beta (Biogen's Avonex®) for multiple sclerosis (MS), imiglucerase (Genzyme's Cerezyme®) for Gaucher's disease,[73] tumor-necrosis factor (TNF) inhibitors (Amgen's Enbrel®, Johnson & Johnson's Remicade®, Abbott Laboratories' Humira®, Biogen's Amevive®, and Genentech's Raptiva®) for autoimmune diseases such as rheumatoid arthritis and psoriasis,[74] and various novel treatments for cancer (including Genentech's Avastin®, Herceptin®, and Rituxan®).[75] Several of these products have become blockbusters and the focus of mass marketing campaigns. Like manufacturers of conventional pharmaceuticals, however, some biotech drug companies have discovered serious adverse events after receiving FDA approval, which may necessitate revised risk labeling or market withdrawal.[76]

¶ 21 In most cases, the FDA classifies a biotech drug as a "biological product," which the statute defines as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the

71. *See* Marc Kaufman, *FDA Approves Wider Use of Growth Hormone*, WASH. POST, July 26, 2003, at A12; *see also* Curtis A. Kin, Note, *Coming to the "Genetic Supermarket" Near You*, 48 STAN. L. REV. 1573 (1996).

72. *See* Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir. 1991) (resolving patent litigation over EPO); Ortho Pharm. Corp. v. Amgen, 709 F. Supp. 504, 506 (D. Del. 1989) (reviewing a contractual dispute based on the breadth of an orphan drug indication for EPO in chronic renal failure). Amgen's Aranesp® (darbepoetin alfa) also belongs to this class of drugs.

73. *See* Ronald Rosenberg, *Genzyme's Plans To Beat Obsolescence*, BOSTON GLOBE, Jan. 8, 1995, at Econ. 57.

74. *See* David P. Hamilton, *New Battleground for Biotech Drugs: Autoimmune Ills*, WALL ST. J., Nov. 5, 2003, at A1; *see also* Marc Kaufman, *Panel Backs Asthma Drug That May Also Help Allergies*, WASH. POST, May 16, 2003, at A1 (describing Xolair, a monoclonal antibody that targets the immunoglobulin E (IgE) antibody, whose imminent FDA approval "will represent a major boost for medical biotechnology, which is increasingly able to adjust the human immune system to prevent diseases and treat chronic conditions"); Gina Kolata, *Drug Is Found To Limit Allergies to Peanuts, Easing Fear of Many*, N.Y. TIMES, Mar. 11, 2003, at A1. Monoclonal antibodies are derived from replications of a single "hybridoma" cell formed by the fusion of a tumor cell and a white blood cell that produces antibodies, which represents a form of genetic modification even though this method did not initially employ recombinant DNA techniques. *See* FDA, Licensing of a Biological Monoclonal Antibody Product Prepared by Hybridoma Technology, 48 Fed. Reg. 50,795 (1983); Chiron Corp. v. Genentech, Inc., 363 F.3d 1247 (Fed. Cir. 2004).

75. *See* David Hamilton, *Genentech Emerges as Leader*, WALL ST. J., May 13, 2005, at B2.

76. *See, e.g.*, Tim Bongartz et al., *Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies*, 295 JAMA 2275 (2006); Andrew Pollack, *M.S. Drug Can Return, with Limits*, N.Y. TIMES, June 6, 2006, at C1 (reporting that the FDA decided to allow "Tysabri [to] return to the market, despite its risk of causing a fatal brain disease, under a program intended to closely monitor doctors who prescribe it and patients who use it"); Andrew Pollack, *Biogen and FDA Issue Drug Warning*, N.Y. TIMES, Mar. 17, 2005, at C3 (reporting that the labeling for the MS drug Avonex® was revised to warn of liver damage); Stephanie Saul, *Johnson & Johnson Adds Data on Deaths to Label on Heart Treatment*, N.Y. TIMES, Apr. 26, 2005, at C4 (Natrecor®); *Three Anemia Drugs May Harm Red Blood Cells*, WASH. POST, Dec. 2, 2005, at A6.

prevention, treatment, or cure of a disease or condition of human beings."[77] Although this differentiates biotech drugs from most other "drugs" under the agency's jurisdiction, the FDA subjects them to a nearly identical review process,[78] and a few years ago it shifted those responsibilities from its smaller Center for Biologics Evaluation & Research (CBER) to its Center for Drug Evaluation & Research (CDER).[79]

¶ 22 In contrast to well-established manufacturers of conventional pharmaceuticals, biotechnology pioneers took full advantage of the special statutory incentives offered for drugs designed to treat rare diseases.[80] Twenty-five years ago, in order to ensure that companies would not overlook patients suffering from less common conditions, Congress enacted the Orphan Drug Act.[81] Products intended to treat a rare disease or condition

77. 42 U.S.C. § 262(i) (2000); *see also* United States v. Loran Med. Sys., Inc., 25 F. Supp. 2d 1082 (C.D. Cal. 1997); Edward L. Korwek, *Human Biological Drug Regulation: Past, Present, and Beyond the Year 2000*, 50 FOOD & DRUG L.J. S123 (1995). Biotechnology-derived products also may qualify as medical devices under the FDA's jurisdiction, particularly in vitro diagnostics. *See* Anny Huang, *FDA Regulation of Genetic Testing: Institutional Reluctance and Public Guardianship*, 53 FOOD & DRUG L.J. 555, 587-89 (1998).

78. *See* 64 Fed. Reg. 56,441, 56,441-42, 56,450-52 (1999) (codified in scattered sections of 21 C.F.R. pt. 601) (amending the regulations to replace separate applications for product and establishment licensing with a single biologics license application (BLA)); 61 Fed. Reg. 24,227, 24,232-33 (1996) (amending the regulations to exempt certain well-characterized biotechnology products from separate establishment licensing application requirement). Some industry insiders have complained that the agency issues nothing more formal than draft guidance documents to announce its policies for reviewing these products. *See* Martha J. Carter, *The Ability of Current Biologics Law To Accommodate Emerging Technologies*, 51 FOOD & DRUG L.J. 375, 376 (1996) ("While the FDA has made a good faith effort to provide guidance to industry and to solicit industry's feedback, it is disquieting to note that the entire field of biotechnology is being regulated without notice and comment rulemaking."); *id*. at 377 (noting that "[g]uidelines are much easier to change than regulations"). This hardly distinguishes biopharmaceuticals, however, from any of the other products subject to the FDA's jurisdiction. *See* Lars Noah, *The FDA's New Policy on Guidelines: Having Your Cake and Eating It Too*, 47 CATH. U. L. REV. 113, 115-24 (1997); *see also* HHS, Annual Comprehensive List of Guidance Documents at the Food and Drug Administration, 70 Fed. Reg. 824 (2005).

79. *See* Marc Kaufman, *FDA Seeks To Hasten Review of Biotech Drugs*, WASH. POST, Sept. 7, 2002, at A3 ("FDA officials said the move makes sense because the testing, evaluation and use of the pharmaceuticals is similar, whether the drugs are created through traditional chemical means or through newer biotechnology. . . . [CBER] will maintain control over vaccines, blood safety, gene therapy and tissue transplantation."). CDER has far more expertise in matters such as the design of clinical trials, and it enjoys greater resources because, until recently, only it had the authority to collect user fees from applicants. *See id*. This move responds in part to direction from Congress that the FDA minimize the differences in product approval requirements applied to drugs and biologics. *See* Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 123(c), 111 Stat. 2324.

80. *See* Marlene E. Haffner, *Orphan Products – Ten Years Later and Then Some*, 49 FOOD & DRUG L.J. 593, 600 (1994) (explaining that "209 of 532 designated orphans were biotechnology-derived products," and predicting that the agency "likely will continue to see a significant number of biotechnology product sponsors applying for orphan status"); Geeta Anand, *How Drugs for Rare Diseases Became Lifeline for Companies*, WALL ST. J., Nov. 15, 2005, at A1.

81. Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa-360ee (2000)); *see also* Baker Norton Pharms., Inc. v. FDA, 132 F. Supp. 2d 30, 31 (D.D.C. 2001) ("Since the passage of the Orphan Drug Act, the FDA has approved at least 172 orphan drugs and biological products . . . ."); David D. Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?*, 55 FOOD & DRUG L.J. 125 (2000); Naomi Aoki, *The Price of Success: Orphan Drug Act Has Spurred Advances – and Disputes*, BOSTON GLOBE, July 25, 2001, at F1.

may qualify for "orphan drug" designation, which entitles the sponsor to certain special incentives: federal grants and tax breaks for conducting clinical trials as well as an extended period of market exclusivity to help companies recoup their investment.[82] Once it approves an orphan drug, the agency must wait seven years before it can green light another company's application to market the "same" drug unless the second applicant can demonstrate the "clinical superiority" of its product.[83]

¶ 23 In the mid-1980s, two manufacturers sought orphan drug approval for recombinant hGH for the treatment of growth hormone deficiency in children. Previously, companies had derived hGH from the pituitary glands of human cadavers, but they withdrew these products after contamination incidents triggered a fatal neurological disease.[84] Almost one year after approving Genentech's r-hGH product (Protropin®), which is derived from genetically engineered *E. coli* bacteria and differed from the natural protein only in the addition of a terminal methionine amino acid group, the FDA approved Eli Lilly's r-hGH product (Humatrope®), which had a protein structure identical to natural hGH. Genentech challenged the agency's decision as unlawfully interfering with its right to seven years of marketing exclusivity.[85] The court sided with Eli Lilly, concluding that Humatrope qualified for orphan drug designation because it differed from the previously approved *natural* hGH products by virtue of the synthetic process used to produce it, which avoided the risk of contamination and filled an unmet need occasioned by their withdrawal from the market.[86] The court declined, however, to address the separate and seemingly trickier question of whether Humatrope differed sufficiently from Protropin, by virtue of its lack of an added methionyl group, to permit approval before the expiration of Genentech's market exclusivity period.[87]

¶ 24 Almost one decade later, a court dealt with this unresolved question simply by deferring to the agency's regulations in the course of upholding the FDA's decision to approve Biogen's drug Avonex®, an interferon beta product used to treat MS.[88] Berlex, which sold a similar orphan drug product (Betaseron®) previously approved by the agency, objected because its seven year exclusivity period had not yet expired. The court sustained the FDA's finding that Avonex was not the same drug because it completely avoided one of the side effects (injection site necrosis) associated with Betaseron, disregarding Berlex's response that the overall safety profiles for the two products were

82. *See* 21 U.S.C. §§ 360cc, 360ee (2000); 26 U.S.C. § 45C (2000). A disease qualifies as "rare" if it affects fewer than 200,000 individuals in the United States. *See* 21 U.S.C. § 360bb(a)(2)(A).

83. *See* 21 C.F.R. §§ 316.3(b)(3)&(13), 316.31 (2006); *see also* Robert A. Bohrer & John T. Prince, *A Tale of Two Proteins: The FDA's Uncertain Interpretation of the Orphan Drug Act*, 12 HARV. J.L. & TECH. 365, 383-95, 414-17 (1999); Edmund L. Andrews, *Kidney Drug Setback for Genetics Institute*, N.Y. TIMES, Jan. 15, 1991, at D4 (reporting that the FDA rejected a second application for EPO after approving Amgen's orphan drug product).

84. *See* Paul Brown et al., *Potential Epidemic of Creutzfeldt-Jakob Disease from Human Growth Hormone Therapy*, 313 NEW ENG. J. MED. 728 (1985).

85. *See* Genentech, Inc. v. Bowen, 676 F. Supp. 301, 306-07 (D.D.C. 1987).

86. *See id*. at 312-13.

87. *See id*. at 313.

88. *See* Berlex Labs., Inc. v. FDA, 942 F. Supp. 19 (D.D.C. 1996).

comparable.[89] Five years later, however, Biogen faced the prospect that a competitor would trump its victory over Berlex.[90]

¶ 25 The most recent biotech orphan drug controversy involved a treatment for Fabry disease. Two companies developed recombinant versions of alpha-galactosidase, an enzyme missing in patients with this rare and fatal condition: Genzyme's Fabrazyme® and Transkaryotic Therapies' Replagal®. Both sponsors had received orphan product designations, and, in an apparently unprecedented situation, both filed their applications for approval within weeks of one another, attempting to take advantage of the less demanding evidence of effectiveness required under the agency's accelerated new drug approval process.[91] An FDA advisory committee found weaknesses in the clinical trial results submitted with both applications, which some observers attributed to the "winner-take-all" aspect of the orphan drug rules that created pressures for each sponsor to rush its studies in an effort to beat the other to market, but the committee concluded that Genzyme had offered a somewhat stronger showing of effectiveness.[92] The agency approved Fabrazyme a few months later.[93]

2. Agricultural Applications and "Frankenfood"

¶ 26 In 1994, Calgene began marketing the FLAVR SAVR™ tomato, a fruit engineered to remain on the vine longer, have a longer retail shelf life, and exhibit improved viscosity in processed foods.[94] Calgene had created the FLAVR SAVR by using a recombinant DNA technique, specifically by isolating the polygalacturonase gene, which is responsible for producing the enzyme that breaks down pectin in the cell walls of the tomato during the ripening process, and reintroducing the gene into the plant (using the soil bacterium *Agrobacterium tumefaciens* as a vector) in the reverse or "antisense" orientation.[95] The antisense copy suppresses the production of the polygalacturonase enzyme. In this respect, Calgene's process simply rearranged the tomato's own genetic material (it was not replaced by material from a different

89. *See id*. at 23-24; *see also* Bohrer & Prince, *supra* note 83, at 395-401 (elaborating on this dispute).

90. *See* Ronald Rosenberg, *Serono Says Drug Better for Skirting Relapses*, BOSTON GLOBE, May 9, 2001, at 4 (reporting that a comparative efficacy trial demonstrated that a new interferon beta product was clinically superior to Avonex in treating MS patients).

91. *See* Naomi Aoki, *FDA Review Deals Blow to TKT: Drug Panel Says Replagal Clinical Data Do Not Justify Approval*, BOSTON GLOBE, Jan. 15, 2003, at D1.

92. *See id*.; *see also* Ron Winslow et al., *Cancer Research Gets a Boost from New Methods of Treatment*, WALL ST. J., June 2, 2003, at A1 (reporting that sponsors have gamed the system).

93. *See* Marc Kaufman, *FDA Approves "Orphan" Drug for Life-Threatening Disorder*, WASH. POST, Apr. 25, 2003, at A9 ("The approval of Fabrazyme is significant in regulatory terms because the drug was classified as a priority (because there is no existing treatment) and an orphan drug, and because it is made with recombinant DNA technology. The FDA's processes for reviewing all three categories of drugs have been hotly debated in recent years.").

94. *See First Biotech Tomato Marketed*, FDA CONSUMER, Sept. 1994, at 3, 4. The tomato was not a commercial success, however, thanks in part to problems with distribution. *See* Terzah Ewing, *Monsanto Buys Rest of Calgene for $240 Million*, WALL ST. J., Apr. 2, 1997, at B5.

95. *See* Calgene, Inc.; Availability of Letter Concluding Consultation, 59 Fed. Reg. 26,647 (1994); *see also* Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1368 (Fed. Cir. 1999) (rejecting the claim that this tomato infringed a patent on antisense technology).

organism), and it reduced the levels of an existing protein (it did not introduce a new chemical or increase the levels of other naturally-occurring substances in the tomato).

¶ 27 The process required the insertion of a selectable "marker" gene, in this case the commonly used kanamycin resistance (*kan*^{r}) gene derived from certain bacteria. Marker genes help to identify those plant cells that have successfully taken up the transferred gene controlling a desired trait; in this case, cells that contain the *kan*^{r} gene synthesize a protein, aminoglycoside 3'-phosphotransferase II (APH(3')II), which renders the cell resistant to the action of antibiotics.[96] By adding kanamycin or a similar antibiotic to the laboratory growth medium, a researcher can screen out the tomato plant cells with unsuccessful gene transfers. Although the marker gene serves no useful purpose beyond that point, it remains part of the genetic material in every cell of the growing transgenic plant.

¶ 28 After the completion of field testing authorized by APHIS,[97] Calgene petitioned the FDA to issue advisory opinions on the regulatory status of the *kan*^{r} gene[98] and the FLAVR SAVR tomato.[99] Later, after the FDA's 1992 publication of a policy statement on foods derived from new plant varieties,[100] the company converted this request into a petition seeking food additive approval of the protein from the *kan*^{r} gene as a processing aid.[101]

¶ 29 In 1994, following a meeting of its Food Advisory Committee, the FDA responded to Calgene's petitions. First, it "concluded that FLAVR SAVR™ tomatoes have not been significantly altered when compared to varieties of tomatoes with a history of safe use."[102] Although not stated in such terms, the FDA in effect found that this tomato was generally recognized as safe (GRAS) and, therefore, not technically a "food additive" when used in processed foods.[103] The agency had once before approved such a

96. *See* Secondary Direct Food Additives Permitted in Food for Human Consumption; Food Additives Permitted in Feed and Drinking Water of Animals; Aminoglycoside 3'-Phosphotransferase II, 59 Fed. Reg. 26,700, 26,702 (1994).

97. *See* Interpretive Ruling on Calgene, Inc.; Petition for Determination of Regulatory Status of FLAVR SAVR™ Tomato, 57 Fed. Reg. 47,608 (1992) (ruling that Calgene's tomato would no longer be considered a regulated article under the Federal Plant Pest Act); *see also* David J. Earp, Comment, *The Regulation of Genetically Engineered Plants: Is Peter Rabbit Safe in Mr. McGregor's Transgenic Vegetable Patch*, 24 ENVTL. L. 1633, 1658-71 (1994) (discussing the APHIS decision and subsequent modifications of its regulations). Calgene subsequently received similar rulings on several other tomato lines. *See, e.g.*, Addition of Two Genetically Engineered Tomato Lines to Determination of Non-Regulated Status for Calgene, Inc., 60 Fed. Reg. 38,788 (1995).

98. *See* Calgene, Inc.; Request for Advisory Opinion, 56 Fed. Reg. 20,004 (1991).

99. *See* Calgene, Inc.; Request for Advisory Opinion, 57 Fed. Reg. 22,772, 22,773 (1992) (noting that Calgene's primary interest in the choice of regulatory classification was whether the company would have to prepare an environmental assessment).

100. *See* Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. 22,984 (1992). This policy is discussed more fully below.

101. *See* Calgene, Inc.; Filing of Food Additive Petition, 58 Fed. Reg. 38,429 (1993).

102. *See* Calgene, Inc.; Availability of Letter Concluding Consultation, 59 Fed. Reg. 26,647, 26,648 (1994).

103. *See id*. at 26,648 (citing 21 C.F.R. § 170.30(f)(2), the provision in the regulations which provides that substances of natural biological origin widely consumed prior to 1958 but then significantly altered through selective breeding will be reviewed for possible GRAS affirmation); *see also* Frederick H.

GRAS affirmation petition – for bioengineered chymosin used in making cheese and other products and as a substitute for the animal-derived version of this milk-clotting enzyme that itself previously had been affirmed as GRAS.[104]

¶ 30 Second, the FDA granted Calgene's food additive petition, approving the use of APH(3')II encoded by the *kan*^{r} gene as a processing aid for developing certain new plant varieties.[105] The agency concluded that the protein expressed by the *kan*^{r} gene is neither toxic nor allergenic and that estimated dietary exposure would be extremely low.[106] Although it provides antibiotic resistance and could, therefore, interfere with the therapeutic use of human antibiotics, the FDA found that the protein would be inactivated and degraded by digestion or heating.[107] Finally, the agency concluded that the proposed additive created no risk of horizontal transfer of the *kan*^{r} gene (and the spread of antibiotic resistance) into human cells lining the intestinal walls or into microorganisms found in the intestines or in the soil.[108]

¶ 31 The Calgene petitions provided a major impetus for the FDA to formulate a general policy governing the regulation of food products produced using biotechnology. In 1992, following immediately in the wake of OSTP's notice concerning the exercise of discretion by the different agencies involved in the regulation of biotechnology,[109] the

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Degnan, *Rethinking the Applicability and Usefulness of the GRAS Concept*, 46 FOOD DRUG COSM. L.J. 553, 580-81 (1991) (urging greater reliance on the GRAS exception for bioengineered foods). The tomato itself would not be subject to regulation as a "food additive" when sold as produce, even if not GRAS.

104. *See* Direct Food Substances Affirmed as Generally Recognized as Safe; Chymosin Enzyme Preparation Derived from Escherichia Coli D-12, 55 Fed. Reg. 10,932, 10,935 (1990) (codified at 21 C.F.R. § 184.1685 (2006)); *see also* Enzyme Bio-Systems, Ltd.; Filing of Petition for Affirmation of GRAS Status, 53 Fed. Reg. 16,191 (1988) (rDNA alpha-amylase enzyme); CPC Int'l, Inc.; Filing of Petition for Affirmation of GRAS Status, 51 Fed. Reg. 10,571 (1986) (same); U.S. CONG., GENERAL ACCOUNTING OFFICE, FOOD SAFETY AND QUALITY: INNOVATIVE STRATEGIES MAY BE NEEDED TO REGULATE NEW FOOD TECHNOLOGIES, No. RCED-93-142 (1993), at 42 [hereinafter GAO, NEW FOOD TECHNOLOGIES] (noting that the FDA's review of the GRAS affirmation petition for chymosin took 2.5 years and represented "a learning experience for the agency").

105. *See* Secondary Direct Food Additives Permitted in Food for Human Consumption; Food Additives Permitted in Feed and Drinking Water of Animals; Aminoglycoside 3'-Phosphotransferase II, 59 Fed. Reg. 26,700, 26,711 (1994) (codified at 21 C.F.R. §§ 173.170, 573.130 (2006)) (approving APH(3')II encoded by the *kan*r gene for use in the development of genetically modified cotton, oil seed rape, and tomatoes). In the preamble, the FDA emphasized that "[o]nly the translation product of the *kan*r gene, APH(3')II, and not the gene itself, is being regulated as a food additive." *Id*. at 26,701 ("[T]he DNA that makes up the *kan*r gene does not differ from any other DNA and does not itself pose a safety concern as a component of food.").

106. *See id*. at 26,702-03.

107. *See id*. at 26,703-04.

108. *See id*. at 26,704-06. For the agency's latest views on this aspect of bioengineered foods, see Draft Guidance for Industry: Use of Antibiotic Resistance Marker Genes in Transgenic Plants, 63 Fed. Reg. 47,505 (1998). In contrast, several European countries objected to the cultivation of a genetically modified corn because of fears that it would transfer antibiotic resistance to intestinal bacteria. *See* Emma Johnson, *CIBA Faces a Maize of Committees in Europe*, 14 NATURE BIOTECH. 1068 (1996); *see also* McGarity, *supra* note 32, at 424, 505-06 (recommending a prohibition on the use of antibiotic resistance marker genes because apparently they are no longer necessary).

109. *See* Exercise of Federal Oversight Within Scope of Authority: Planned Introduction of Biotechnology Products into the Environment, 57 Fed. Reg. 6753 (1992); *see also supra* notes 35-36 and accompanying text (discussing this policy). Evidently, the President's Council on Competitiveness, which

FDA announced a policy statement on foods derived from new plant varieties,[110] and it subsequently published notices requesting further public comment on separate aspects of the subject, including appropriate safety testing.[111]

¶ 32 At the outset, the policy statement notes that revolutionary genetic modification techniques – such as recombinant DNA and cell fusion[112] – will lead to the development of new varieties of food plants that would not have been possible using more traditional methods of selective breeding.[113] The agency recognized that "[m]ost, if not all, cultivated food crops have been genetically modified" by traditional breeding techniques.[114] It also noted that, because "these techniques are more precise, they

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had played a central role in the drafting of OSTP's policy, prevailed on the FDA to take a laissez faire approach to GM foods. *See* Warren E. Leary, *Gene-Altered Food Held by the F.D.A. To Pose Little Risk*, N.Y. TIMES, May 26, 1992, at A1.

110. *See* Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. 22,984 (1992); *see also* GAO, NEW FOOD TECHNOLOGIES, *supra* note 104, at 9-10, 31-56 (describing the FDA's approach to the regulation of biotechnology as applied to food, and framing the terms of the debate over the proper regulatory approach); Robert A. Bohrer, *Food Products Affected By Biotechnology*, 55 U. PITT. L. REV. 653, 659-66 (1994) (summarizing the FDA's 1992 policy statement); Henry I. Miller, *Foods of the Future: The New Biotechnology and FDA Regulation*, 269 JAMA 910 (1993). A rudimentary framework previously had been described in the mid-1980s. *See* Jeffrey N. Gibbs & Jonathan S. Kahan, *Federal Regulation of Food and Food Additive Biotechnology*, 38 ADMIN. L. REV. 1, 16-26 (1986); Stephen H. McNamara, *FDA Regulation of Food Substances Produced by New Techniques of Biotechnology*, 42 FOOD DRUG COSM. L.J. 50 (1987); Michele J. Brace, Comment, *Regulation of Genetically Engineered Foods Under the Federal Food, Drug, and Cosmetic Act*, 33 AM. U. L. REV. 899 (1984).

111. *See* Alternative and Traditional Models for Safety Evaluation of Food Ingredients; Announcement of Study; Request for Scientific Data and Information; Announcement of Open Meeting, 61 Fed. Reg. 8291 (1996) (announcing that the Federation of American Societies of Experimental Biology (FASEB) would undertake a comprehensive review of the appropriate scientific criteria and principles for the assessment of the safety of food ingredients, noting that recent innovations such as bioengineering may "present new situations for which an alternative approach to safety assessment may be needed"); *see also* Rick Weiss, *Biotech Food Raises a Crop of Questions*, WASH. POST, Aug. 15, 1999, at A1 (discussing the challenges encountered in efforts to test safety). The 1992 policy statement suggested that "many of the scientific considerations for evaluating the safety and nutritional aspects of food from new plant varieties . . . are similar regardless of the technology used." Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,991.

112. *See* James F. Shepard et al., *Genetic Transfer in Plants Through Interspecific Protoplast Fusion*, 219 SCIENCE 683 (1983); *cf*. Bastian, *supra* note 43, at 440-41 (explaining that commenters persuaded APHIS to exclude protoplast fusion from its regulatory definition of "genetic engineering").

113. *See* Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,984. The policy statement does not address food uses of biotechnology other than in the development of new plant varieties. *See id*.

114. *Id*. at 22,984 n.3; *see also id*. at 22,985 ("The genetic modification techniques used to develop new plant varieties constitute a continuum."); Alan Goldhammer, *The Regulation of Agricultural Biotechnology: An Industrial Perspective*, 48 FOOD & DRUG L.J. 501 (1993); Robert M. Goodman et al., *Gene Transfer in Crop Improvement*, 236 SCIENCE 48, 48-50 (1987) (describing dozens of crops successfully bred across species or genera barriers); Svante Pääbo, *Neolithic Genetic Engineering*, 398 NATURE 194 (1999); David Barboza, *You Asked for It, You Got It: The Pint-Size Watermelon*, N.Y. TIMES, June 15, 2003, § 1, at 1 ("Scientists from the two companies did not need to use genetic engineering . . . . They simply crossed different breeds of watermelon, using the processes that over the last decade have brought [us] orange bell peppers, golden raspberries and broccolini, a cross between Chinese kale and broccoli . . . ."); Adrian Higgins, *Why the Red Delicious No Longer Is: Decades of Makeovers Alter Apple to Its Core*, WASH. POST, Aug. 5, 2005, at A1; Andrew Pollack, *Grant Aims at More Healthful Crops*, N.Y. TIMES, Oct. 21, 2003, at F7.

increase the potential for safe, better-characterized, and more predictable foods."[115] After all, conventional breeding has resulted in some foods with high levels of toxins.[116]

¶ 33 The FDA's policy statement canvassed a variety of potential safety issues posed by genetic modification – some shared with traditional selective breeding and some unique to the new methods – including unexpected chromosomal effects, changes in the levels of naturally occurring toxins in plants, reductions in nutrient bioavailability, production of new substances, introduction of allergens, and increased antibiotic resistance from marker genes.[117] The agency decided, however, that it need not develop a distinctive regulatory approach for foods derived from genetically modified plants. Instead, it preferred to "utiliz[e] an approach identical in principle to that applied to foods developed by traditional plant breeding."[118] The policy statement embraced a functional rather than literal approach to the food additive issue.[119] In short, according to the policy statement, the FDA planned to rely on its enforcement authority under the general adulteration provisions to ensure the safety of whole foods derived from GM plants, though it pointed out that the transferred genetic material and the intended expression products could be subject to regulation as food additives if not GRAS.[120] The agency did not, however, explain how it would become aware of bioengineered foods for which it might require the submission of food additive petitions.

¶ 34 The intended expression product generally will not alter the GRAS status of any

115. Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,986. In discussing genetic modification techniques to achieve desirable traits, the agency distinguished between agronomic characteristics of the plant (e.g., increased yield and resistance to pests or disease) and quality characteristics of the food (e.g., preservation, nutrition, and flavor). *See id*. at 22,985.

116. *See* Warren Ausubel, *Federal Regulation of Genetically Engineered Food Additives and Pesticides*, 4 HIGH TECH. L.J. 114, 124-25 n.52 (1989) (noting the discovery of toxins in potato, grape, and squash cultivars produced through traditional cross-breeding); Declan Butler & Tony Reichhardt, *Long-Term Effect of GM Crops Serves up Food for Thought*, 398 NATURE 651, 652-53 (1999); Cross, *supra* note 59, at 873.

117. *See* Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,986-88 (adding that some of these concerns are magnified with regard to plants used in animal feed because of livestock's different consumption patterns). In its earlier statements, the FDA called for a food additive petition in every case where a substance added to animal feed was produced through rDNA. *See* Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302, 23,311 (1986).

118. Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,984-85 ("The method by which food is produced or developed may . . . 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."); *see also* AMA Council on Scientific Aff., *Biotechnology and the American Agricultural Industry*, 265 JAMA 1429 (1991); John Beringer, *Keeping Watch over Genetically Modified Crops and Foods*, 353 LANCET 605 (1999); Andrew Pollack, *Panel Sees No Unique Risk from Genetic Engineering*, N.Y. TIMES, July 28, 2004, at A13 (summarizing the latest review of this question by the National Academy of Sciences); *Genetically Modified Foods Are Safe, U.N. Agency Says*, ORLANDO SENTINEL, June 24, 2005, at A9 (noting the issuance of a favorable report from the World Health Organization).

119. *See* Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,990 (explaining that it will "require food additive petitions in cases where safety questions exist sufficient to warrant formal premarket review by FDA to ensure public health protection").

120. *See id*. Because nucleic acids appear in the genetic material of all foods and have posed no safety problems in the past, the "FDA does not expect that there will be any serious question about the GRAS status of transferred genetic material." *Id*.

food derived from the new plant variety, unless it is "a protein, carbohydrate, fat or oil, or other substance that differs significantly in structure, function, or composition from substances currently found in food."[121] Thus, if transferred genetic material introduces an unusual protein and/or alters a metabolic pathway to produce a new carbohydrate or other substance, then the FDA may call for the submission of a food additive petition. Furthermore, apart from the possibility that a new component in a whole food might be regulated as a food additive, the whole food itself could be regulated as a food additive when used as a component of a processed food. The agency noted, however, that it rarely has ruled on the GRAS status of a whole food when used as a component in a processed food, e.g., tomatoes in vegetable soup, because most food plants "have been widely recognized and accepted as safe."[122]

¶ 35 The policy statement provided detailed guidance for industry in conducting safety evaluations of new plant varieties and in determining the need for a food additive petition.[123] It also invited companies unsure about a new product's regulatory status to consult with the FDA on an ad hoc basis rather than having to submit a formal petition requesting an advisory opinion.[124] In materials distributed two years later at a meeting of

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121. *Id*. ("For example, if a food derived from a new plant variety contains a novel protein sweetener as a result of the genetic modification of the plant, that sweetener would likely require submission of a food additive petition . . . ."). The policy does not further define what might constitute a significant modification, though similar language appears in the GRAS regulations. *See* 21 C.F.R. § 170.30(f)(2) (2006); *see also* Gibbs & Kahan, *supra* note 110, at 16 n.80 (noting that, "[a]t one point, FDA had proposed that a 'significant alteration' would be a 10% or greater increase in a toxicant or a 20% or greater reduction in a nutrient . . . [but] [t]hese numerical criteria were not adopted").

122. Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,990.

123. *See id*. at 22,991-23,004 (including several flow charts but emphasizing that they do not impose any new regulatory requirements). "This guidance section provides a basis for determining whether new plant varieties are as safe and nutritious as their parental varieties." *Id*. at 22,992; *see also* David A. Kessler et al., *The Safety of Foods Developed by Biotechnology*, 256 SCIENCE 1747 (1992). This sounds like the test of "substantial equivalence" for medical devices under section 510(k) of the FD&C Act to determine the need for premarket review. *See* 21 U.S.C. §§ 360(k), 360c(i)(1) (2000). Indeed, the agency cited international organizations that have proposed a "substantial equivalence" test for new foods. *See* Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,992. The FDA subsequently explained that it had

> used the term "substantial similarity" rather than "substantial equivalence," to avoid possible confusion with the agency use of the concept . . . for medical devices. For consistency with current thinking from international expert groups such as the FAO/WHO and OECD consultation groups, FDA is now using the term "substantial equivalence" with respect to food products.

Substances Generally Recognized as Safe, 62 Fed. Reg. 18,938, 18,945 n.2 (1997); *see also* ORGANIZATION FOR ECONOMIC CO-OPERATION & DEVELOPMENT, SAFETY EVALUATION OF FOODS DERIVED BY MODERN BIOTECHNOLOGY (1993). For a review and critique of the FDA's application of this concept to GM foods, see McGarity, *supra* note 32, at 442-58; *id*. at 454 ("The legality of this aggressive use of the substantial equivalence doctrine depends upon whether Congress meant for the term 'common use in food' in the GRAS exception to encompass not only substances commonly used in foods, but also substances that have never been used in foods but that are 'substantially similar' to substances that have been commonly used in foods.").

124. *See* Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,985. As a consequence, a petitioner may avoid the need to submit an environmental assessment, a potentially significant matter for biotechnology products even though an assessment may have been submitted at an

its Food Advisory Committee, the agency announced its intention to propose a regulation that would require formal premarket notification for all bioengineered foods, including the submission of any available safety and nutritional information to the FDA.[125] The mere "threat" to publish such a proposal prompted numerous companies over the last decade to consult with the agency on the status of bioengineered products that they have under development,[126] and a number of genetically modified foods have reached the market after this informal review process, which sometimes results in the issuance of an FDA "letter of certification."

¶ 36 Although the FLAVR SAVR tomato posed fairly narrow scientific issues, the FDA and Calgene spent considerable time analyzing its safety and debating how best to regulate the product. Newer biotechnological innovations pose more serious regulatory questions than the Calgene tomato. For instance, after an extensive review, the agency did not object to the sale of herbicide-tolerant soybeans.[127] Other GM food crops have enhanced resistance to pests and diseases (in essence, "vaccinated" against viruses), and, in the future, may enjoy tolerance to cold and drought.[128] Agricultural biotech reached a pair of milestones in 2005: planting of the billionth acre of GM seed, though the vast majority of these crops enjoyed improved agronomic characteristics rather than

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earlier stage to the USDA or the EPA. Food additive and GRAS affirmation petitions must either include an environmental assessment or claim a categorical exclusion. *See* 21 C.F.R. §§ 25.22(a)(10)&(12), 25.24(b) (2006).

125. *See* Noah & Merrill, *supra* note 49, at 411.

126. *See, e.g.*, CFSAN, *List of Completed Consultations on Bioengineered Foods* (Nov. 2005), *available at* http://www.cfsan.fda.gov/~lrd/biocon.html (last visited July 14, 2006) (listing more than 50 consultations conducted with various companies since the 1994 Calgene approval). Three years later, the agency issued new guidance. *See* CFSAN, *Guidance on Consultation Procedures: Foods Derived from New Plant Varieties* (Oct. 1997), *available at* http://vm.cfsan.fda.gov/~lrd/consulpr.html (last visited July 14, 2006); *see also* Sheldon Krimsky & Nora K. Murphy, *Biotechnology at the Dinner Table: FDA's Oversight of Transgenic Food*, 584 ANNALS 80, 83 (2002) (discussing these and other revisions, and explaining that the FDA review takes an average of almost six months); Leila Abboud, *Makers of Modified Crops Faulted on Safety Data Submitted to FDA*, WALL ST. J., Jan. 7, 2003, at A3 (reporting criticisms about the rigor of this process). Although it encouraged the use of its proposed GRAS notification procedure, the FDA recognized that the procedure could not fully replace its existing consultation policy for bioengineered foods. *See* Substances Generally Recognized as Safe, 62 Fed. Reg. at 18,946 & n.3.

127. *See* Steven H. Yoshida, *The Safety of Genetically Modified Soybeans: Evidence and Regulation*, 55 FOOD & DRUG L.J. 193, 200 (2000) ("Equivalence of GM soybeans to non-GM soybeans was supported by studies on nutritional composition, lack of toxicity and allergenicity, and suitability as animal feed. Consequently, GM soybeans were approved by FDA as safe for human consumption."); *id*. at 202 ("Although the CP4 EPSPS protein which confers glyphosate [RoundUp®] resistance is present within the soy plant, this protein preferentially accumulates in chloroplasts, not beans. As a result, the CP4 EPSPS is at most a trace component of the soybean."); *cf. id*. at 203-05 (conceding that some questions about these products remain unresolved by the available research). Approximately 85% of all soybeans grown in the United States share this trait. *See* Lamb, *supra* note 26, at 13 (adding that more than half of the corn has similar bioengineered traits).

128. *See* Philip H. Abelson & Pamela J. Hines, *The Plant Revolution*, 285 SCIENCE 367 (1999); Bernard Dixon, *The Paradoxes of Genetically Modified Foods*, 318 BRIT. MED. J. 547 (1999); Steven W. Frank, *Food Additive Models for the Regulation of Recombinant DNA Technology Under the Federal Food, Drug, and Cosmetic Act*, 45 FOOD DRUG COSM. L.J. 169, 173-79 (1990) (describing the range of potential food uses of biotechnology); Lakshman D. Guruswamy, *Sustainable Agriculture: Do GMOs Imperil Biosafety?*, 9 IND. J. GLOBAL LEGAL STUD. 461, 469-74 (2002); Leighton Jones, *Science, Medicine and the Future: Genetically Modified Foods*, 318 BRIT. MED. J. 581 (1999).

nutritional or other features of direct benefit to consumers,[129] and the first completed sequencing of a food plant's genome, which promises to facilitate more ambitious efforts at both conventional breeding and genetic engineering.[130]

¶ 37 On the down side, researchers have identified unexpected allergens in soybeans engineered for higher protein content.[131] Initial animal studies have suggested that potatoes made more resistant to pests by the insertion of a lectin gene caused immune suppression.[132] Mustard plants bioengineered for herbicide tolerance had a greater tendency for interbreeding with wild varieties.[133] Recently completed British field trials have found that winter oil seed rape modified for herbicide tolerance leads to farming practices that adversely impact the populations of insects and birds (though partly because improved weed control reduces foodstuffs available for wildlife),[134] but other

129. *Billionth Acre of Biotech Seed Is Planted, Reports Trade Group*, SAN JOSE MERCURY NEWS, May 9, 2005 (referring to global figures); *see also* Rachel Melcer, *Study Says Farmers Benefiting from Higher Yields and Lower Costs*, ST. LOUIS POST-DISPATCH, Dec. 7, 2005, at B1; *cf.* Anne Fitzgerald, *Building a Healthier Bean: Pioneer Hi-Bred International Develops Seeds To Produce More Crops That Benefit Consumers' Well-Being*, DES MOINES REG., Sept. 25, 2005. Biotechnology also has impacted non-food crops such as cotton and timber. *See, e.g.*, Dan Ferber, *Risks and Benefits: GM Crops in the Cross Hairs*, 286 SCIENCE 367 (1999) (reporting that cotton engineered for insect resistance reduced the use of pesticides in the U.S. by more than one million pounds annually). Researchers even have tried engineering a fungus to destroy an unwanted cash crop. *See* Rick Bragg, *A Fungus To Kill Marijuana Has Environmentalists Wary*, N.Y. TIMES, July 27, 1999, at A1.

130. *See* Justin Gillis, *Rice Genome Fully Mapped: First DNA Map for a Crop Expected To Boost Modification Efforts*, WASH. POST, Aug. 11, 2005, at A1; *see also* Peter N. Spotts, *A Food Revolution Beckons, but Few Show up*, CHRISTIAN SCI. MONITOR, Aug. 15, 2005, at 1 (discussing obstacles to commercialization). Even before this breakthrough, researchers had engineered rice to have enhanced nutritional characteristics. *See* Dennis Normile, *Monsanto Donates Its Share of Golden Rice*, 289 SCIENCE 843 (2000); Christopher Marquis, *Monsanto Plans to Offer Rights To Its Altered-Rice Technology*, N.Y. TIMES, Aug. 4, 2000, at A11 (discussing "golden rice," a beta-carotene rich product made through a complex multigene transfer process and promising to help combat vitamin A deficiency in developing countries).

131. *See* Julie A. Nordlee et al., *Identification of a Brazil-Nut Allergen in Transgenic Soybeans*, 334 NEW ENG. J. MED. 688 (1996); Ron Winslow, *Allergen Is Inadvertently Transferred to Soybean in Bioengineering Test*, WALL ST. J., Mar. 14, 1996, at B6 (reporting that "the findings provide fuel to critics who contend that altering the genes of plants . . . raises the possibility of unintended . . . health consequences"); *see also* Rick Weiss, *Allergy, Engineered Pea Linked*, WASH. POST, Nov. 28, 2005, at A8.

132. *See* Martin Enserink, *Preliminary Data Touch Off Genetic Food Fight*, 283 SCIENCE 1094 (1999); Peta Firth, *Leaving a Bad Taste*, SCI. AM., May 1999, at 34; *see also* Stephen Clapp, *Monsanto Defends Corn Variety Against Safety Accusations*, FOOD CHEM. NEWS, May 30, 2005, at 5 (reporting that internal company research purportedly found smaller kidneys and altered blood composition in lab rats fed corn engineered to resist rootworm infestations).

133. *See* J. Bergelson et al., *Promiscuity in Transgenic Plants*, 395 NATURE 25 (1998); Kathryn Brown, *Seeds of Concern*, SCI. AM., Apr. 2001, at 54; James Kling, *Could Transgenic Supercrops One Day Breed Superweeds*, 274 SCIENCE 180 (1996); Thomas R. Mikkelsen et al., *The Risk of Crop Transgene Spread*, 380 NATURE 31 (1996); Carol Kaesuk Yoon, *When Biotechnology Crops and Their Wild Cousins Mingle*, N.Y. TIMES, Nov. 3, 1999, at A18; *see also* Frances E. Sharples, *Regulation of Products from Biotechnology*, 235 SCIENCE 1329 (1987) (warning of adverse ecological effects); Andrew Pollack, *Genes from Engineered Grass Spread for Miles, Study Finds*, N.Y. TIMES, Sept. 21, 2004, at A1 (discussing EPA research of herbicide-resistant bentgrass that pollinated wild strains up to 13 miles downwind).

134. *See* Paul Brown & David Gow, *Damning Verdict on GM Crop: Final Report on World's Most Comprehensive Field Trials Say Oil Seed Rape Varieties Would Harm Wildlife and the Environment*, GUARDIAN (London), Mar. 22, 2005, at 9; *see also* John E. Losey, *Transgenic Pollen Harms Monarch*

researchers have highlighted the ecological advantages that would accompany the use of GM food crops.[135]

¶ 38 Whatever the rigor of the premarket review process, regulatory problems may arise after initial agency clearance. For instance, StarLink™ corn, genetically engineered to express the Cry9c protein, one of the many toxins produced by the soil bacterium *Bacillus thuringiensis* (Bt),[136] was approved by the EPA only for use in animal feed.[137] Nonetheless, it entered the human food supply through accidental cross-pollination, resulting in a widely publicized recall of products such as tortillas made from the contaminated flour.[138] Although a number of exposed consumers complained of hives

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Larvae, 399 NATURE 214 (1999); Deepak Saxena, *Insecticidal Toxin in Root Exudates from Bt Corn*, 402 NATURE 480 (1999). It should not be forgotten, however, that chemical pesticide applications pose a far more serious threat to non-target species, including beneficial insects. *See* Hal Bernton, *Hostile Market Spells Blight for Biotech Potatoes*, SEATTLE TIMES, Apr. 30, 2000, at A1 (discussing a Bt-modified potato). The study involving Monarch butterfly caterpillars received a great deal of public attention but ultimately seemed to be overblown. *See* Carol Kaesuk Yoon, *Biotech Corn Isn't Serious Threat to Monarchs, Draft U.S. Report Finds*, N.Y. TIMES, Sept. 26, 2000, at F4. Another widely publicized report of cross-pollination originally published in the journal *Nature* also proved in retrospect to be seriously exaggerated. *See* Nick Kaplinsky et al., *Maize Transgene Results in Mexico Are Artifacts*, 416 NATURE 601 (2002); Eric Hand, *Biotech Corn Hasn't Mixed with Maize in Mexico, Study Says*, ST. LOUIS POST-DISPATCH, Aug. 9, 2005, at A3.

135. *See* L.L. Wolfenbarger & P.R. Phifer, *The Ecological Risks and Benefits of Genetically Engineered Plants*, 290 SCIENCE 2088 (2000) (discussing the advantages of reduced pesticide and herbicide use as well as less habitat destruction because of improved yields on land already converted to agricultural purposes); *see also* Alan W. Dove, *Clone on the Range: What Animal Biotech Is Bringing to the Table*, 23 NATURE BIOTECH. 283, 285 (2005) (describing the "EnviroPig," which is designed to reduce problems with run-off by producing manure containing 30% less phosphorous); Sara M. Dunn, *From Flav'r Sav'r to Environmental Saver? Biotechnology and the Future of Agriculture, International Trade, and the Environment*, 9 COLO. J. INT'L ENVTL. L. & POL'Y 145 (1998); Rachel Melcer, *Study Touts Benefits of Genetically Modified Crops*, ST. LOUIS POST-DISPATCH, Oct. 12, 2005, at F2.

136. Bt serves as a biological pesticide, but it degrades rapidly when applied by spraying, which scientists have overcome by genetically modifying plants to express the toxins produced by Bt. *See* Fred S. Betz et al., *Safety and Advantages of Bacillus Thuringiensis-Protected Plants To Control Insect Pests*, 32 REG. TOXICOLOGY & PHARMACOLOGY 156 (2000). The EPA has noted concerns about the spread of resistance to Bt. *See* Plant Pesticides Resistance Management: Notice of Meeting, 62 Fed. Reg. 19,115 (1997). The latest research is, however, fairly reassuring on this score. *See* Bruce E. Tabashnik et al., *Delayed Resistance to Transgenic Cotton in Pink Bollworm*, 102 PROC. NAT'L ACAD. SCI. 15,389 (2005).

137. *See* Allergenicity Assessment of Xry9C Bt Corn Plant Pesticide, 64 Fed. Reg. 71,452 (1999); *see also* Sutter v. Aventis CropScience USA Holding, Inc., 145 F. Supp. 2d 1050, 1052 (S.D. Iowa 2001); Rick Weiss, *EPA Restricts Gene-Altered Corn in Response to Concerns: Farmers Must Plant Conventional "Refuges" To Reduce Threat of Ecological Damage*, WASH. POST, Jan. 16, 2000, at A2.

138. *See* Rebecca M. Bratspies, *Myths of Voluntary Compliance: Lessons from the StarLink Corn Fiasco*, 27 WM. & MARY ENVTL. L. & POL'Y REV. 593 (2003); D.L. Uchtmann, *Starlink™: A Case Study of Biotechnology Agricultural Regulation*, 7 DRAKE J. AGRIC. L. 159 (2002); *see also* Andrew Pollack, *1999 Survey on Gene-Altered Corn Disclosed Some Improper Uses*, N.Y. TIMES, Sept. 4, 2001, at C2 (reporting that the agency and the company had evidence of potential contamination before it was revealed by the testing of taco shells). After this incident, the EPA stopped granting "split" pesticide registrations (i.e., distinguishing between crops for animal and human consumption). *See* Opportunity To Comment on Implications of Revised Bt Crops Reassessment for Regulatory Decisions Affecting These Products, and on Potential Elements of Regulatory Options, 66 Fed. Reg. 37,227 (2001); David Barboza, *Gene-Altered Corn Changes Dynamics of Grain Industry*, N.Y. TIMES, Dec. 11, 2000, at A1; Andrew Pollack, *Aventis Gives up License To Sell Bioengineered Corn*, N.Y. TIMES, Oct. 13, 2000, at C5. USDA also promised to improve

and other allergic reactions, the U.S. Centers for Disease Control and Prevention (CDC) found no link to the tainted products,[139] but the economic losses allegedly suffered by farmers, food processors and retailers led to extensive litigation.[140]

¶ 39 The FDA repeatedly has rejected suggestions that all bioengineered foods disclose their origin in labeling.[141] Primarily representing a scientific judgment and legal conclusion that no justification existed for mandating routine disclosures, the decision also reflected the sheer impracticality of keeping track of GMOs in the food supply.[142] The agency said it would require disclosure, however, if the insertion of genetic material from another source introduced a risk of allergenicity.[143]

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the rigor of its review process. *See* David Barboza, *Monsanto Faces Growing Skepticism on Two Fronts*, N.Y. TIMES, Aug. 5, 1999, at C1.

139. *See* Assessment of Scientific Information Concerning StarLink Corn Cry9C Bt Corn Plant-Pesticides, 65 Fed. Reg. 65,246 (2000); Marc Kaufman, *Biotech Corn Is Test Case for Industry: Engineered Food's Future Hinges on Allergy Study*, WASH. POST, Mar. 19, 2001, at A1; *see also* Rita Batista et al., *Lack of Detectable Allergenicity of Transgenic Maize and Soya Samples*, 116 J. ALLERGY & CLIN. IMMUNOLOGY 403 (2005). The advocacy group Greenpeace recently attempted to generate a similar scare overseas. *See* David Barboza, *Illegal Rice Found Again in China's Food Supply*, N.Y. TIMES, June 14, 2005, at C6.

140. *See In re* StarLink Corn Prods. Liab. Litig., 212 F. Supp. 2d 828 (N.D. Ill. 2002); *In re* StarLink Corn Prods. Liab. Litig., 152 F. Supp. 2d 1378 (J.P.M.L. 2001); Dupraz v. Aventis CropScience USA Holding, Inc., 153 F. Supp. 2d 1102 (D.S.D. 2001); David Barboza, *Negligence Suit Is Filed over Altered Corn*, N.Y. TIMES, Dec. 4, 2000, at C2; *see also* Andrew Harris, *Genetic Corn: Danger Uncertain, but Suits Multiply*, NAT'L L.J., Sept. 9, 2002, at A12 (reporting that the lawsuits filed by consumers settled for $9 million).

141. *See* J. Howard Beales III, *Modification and Consumer Information: Modern Biotechnology and the Regulation of Information*, 55 FOOD & DRUG L.J. 105 (2000) (defending this policy); Fred H. Degnan, *Biotechnology and the Food Label: A Legal Perspective*, 55 FOOD & DRUG L.J. 301 (2000); Margaret Gilhooley, *Reexamining the Labeling for Biotechnology in Foods: The Species Connection*, 82 NEB. L. REV. 1088, 1105-17 (2004) (proposing mandatory disclosure in limited circumstances); *id*. at 1091 ("The best case for additional labeling is when a gene has been transferred from a different plant or animal species [a so-called "wide cross"] to a food to affect its taste or nutrition [as opposed to serving agronomic purposes]."); Karen A. Goldman, *Labeling of Genetically Modified Foods: Legal and Scientific Issues*, 12 GEO. INT'L ENVTL. L. REV. 717, 757-60 (2000) (defending the FDA's policy); Michael A. Whittaker, Comment, *Reevaluating the Food and Drug Administration's Stand on Labeling Genetically Engineered Foods*, 35 SAN DIEGO L. REV. 1215 (1998).

142. *See* Henry I. Miller, *A Rational Approach to Labeling Biotech-Derived Foods*, 284 SCIENCE 1471, 1472 (1999) (explaining that GM produce "would have to be segregated throughout all phases of production (planting, harvesting, processing, and distribution)"); Nigel Williams, *Can Regulations Requiring Labeling of Genetically Modified Foods Work?*, 281 SCIENCE 769 (1998); Lara Beth Winn, *Special Labeling Requirements for Genetically Engineered Food: How Sound Are the Analytical Frameworks Used by FDA and Food Processors*, 54 FOOD & DRUG L.J. 667 (1999); Patricia Callahan, *Some Ingredients Are Genetically Modified Despite Label Claims*, WALL ST. J., Apr. 5, 2001, at A1; Kurt Eichenwald, *New Concerns Rise on Keeping Track of Modified Corn*, N.Y. TIMES, Oct. 14, 2000, at A1; Rick Weiss, *Food War Claims Its Casualties: High-Tech Crop Fight Victimizes Farmers*, WASH. POST, Sept. 12, 1999, at A1.

143. *See* Food Labeling; Foods Derived from New Plant Varieties, 58 Fed. Reg. 25,837, 25,840 (1993) ("Under FDA's policy, such foods will be required to be labeled to alert consumers to potential allergenic substances derived from commonly allergenic foods, unless the developer can demonstrate scientifically that the introduced substance is not allergenic in the new food.").

For example, if a tomato has had a peanut protein introduced into it and there is insufficient information to demonstrate that the introduced protein could not cause an allergic reaction in a susceptible population, a

¶ 40 The labeling question became extremely contentious in the wake of the agency's 1993 approval of the new animal drug Posilac® (recombinant bovine somatotropin (rBST)).[144] Because it could detect no difference between milk from cows administered rBST and other milk, the FDA did not require any special disclosure statement in labeling.[145] At the same time, it declined to prohibit non-misleading claims that a dairy product was derived from cows that had not received rBST.[146] In 2001, the FDA issued new guidelines dealing with voluntary labeling of GM or non-GM foods, but it continued to abide by its earlier conclusion not to mandate disclosure.[147]

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label declaration would be required to alert consumers who are allergic to peanuts so they could avoid that tomato . . . .

Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. at 22,991; *cf.* H.R. 5401, 102d Cong. (1992) (proposing to require disclosures of origin in labeling). Congress recently mandated clearer allergenicity labeling of processed foods. *See* Food Allergen Labeling and Consumer Protection Act of 2004, Pub. L. No. 108-282, tit. II, 118 Stat. 891 (to be codified at 21 U.S.C. § 343(w)); Sally Squires, *New Look for Food Labels*, WASH. POST, Jan. 10, 2006, at F1; *see also* Cindy Skrzycki, *Allergy Fears Tinge Debate on Bug-Dye Rule*, WASH. POST, May 9, 2006, at D1 (reporting that the agency's proposed rule responds to dozens of severe allergic reactions associated with certain natural color additives derived from insects that are used in foods and cosmetics).

144. *See* Animal Drugs, Feeds, and Related Products; Sterile Sometribove Zinc Suspension, 58 Fed. Reg. 59,946, 59,947 (1993) (codified at 21 C.F.R. § 522.2112 (2006)); *see also* David Aboulafia, *Pushing RBST: How the Law and the Political Process Were Used To Sell Recombinant Bovine Somatotropin to America*, 15 PACE ENVTL. L. REV. 603, 614-54 (1998) (criticizing numerous aspects of this decision, and arguing more generally that it illustrates the flaws with existing federal policies governing biotechnology); Dan L. Burk, *The Milk Free Zone: Federal and Local Interests in Regulating Recombinant BST*, 22 COLUM. J. ENVTL. L. 227 (1997) (defending the agency's decision). In contrast, Canadian officials subsequently declined to approve the product, and the EU banned milk produced from cows given the drug. *See* Jennifer R. Thornley, Note, *Got "Hormone-Free" Milk?: Your State May Have Enough Interest To Let You Know*, 76 IND. L.J. 785, 791-92 (2001).

145. *See* Interim Guidance on the Voluntary Labeling of Milk and Milk Products from Cows That Have Not Been Treated with Recombinant Somatotropin, 59 Fed. Reg. 6279 (1994).

146. *See id.*; *see also* Stauber v. Shalala, 895 F. Supp. 1178, 1192-93 (W.D. Wis. 1995) (rejecting challenge to the FDA's decision against mandating rBST disclosure in labeling); Terence J. Centner & Kyle W. Lathrop, *Labeling rbST-Derived Milk Products: State Responses to Federal Law*, 45 U. KAN. L. REV. 511 (1997); Anne Miller, *Time for Government to Get Mooo-ving: Facing up to the BST Labeling Problem*, 18 HAMLINE L. REV. 503 (1995). Producers challenged Vermont's rBST disclosure requirement as an abridgement of their First Amendment rights, and the courts granted them a preliminary injunction. *See* Int'l Dairy Foods Ass'n v. Amestoy, 92 F.3d 67 (2d Cir. 1996); *see also* Kathleen Lennon, Note, *Government's Udder Disregard for a Consumer's Right to Information on rBST: Mandatory Labeling for Milk Products Should Be Allowed*, 22 VT. L. REV. 433 (1997). *See generally* Lars Noah, *What's Wrong with "Constitutionalizing Food and Drug Law"?*, 75 TUL. L. REV. 137 (2000). Conversely, retailers challenged laws in other states that purportedly forbid the use of rBST-free labeling. *See* Beth Berselli, *Settlement Reached in Hormone Labeling Case: Ben & Jerry's, States Agree Food Makers Can Indicate Absence of Added Product*, WASH. POST, Aug. 15, 1997, at A22.

147. *See* Draft Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering, 66 Fed. Reg. 4839 (2001); *see also* Carl R. Galant, Comment, *Labeling Limbo: Why Genetically Modified Foods Continue To Duck Mandatory Disclosure*, 42 HOUS. L. REV. 125 (2005); Kelly A. Leggio, Comment, *Limitations on the Consumer's Right to Know: Settling the Debate over Labeling of Genetically Modified Foods in the United States*, 38 SAN DIEGO L. REV. 893, 948-50 (2001) (defending the FDA's policy); Frank J. Miskiel, Comment, *Voluntary Labeling of Bioengineered Food: Cognitive Dissonance in the Law, Science, and Public Policy*, 38 CAL. W. L. REV. 223, 247-54 (2001) (recommending restrictions on voluntary "non-GMO" labeling).

¶ 41 The Department of Agriculture also has struggled with labeling issues related to GM foods. As the agency responsible for implementing the Organic Foods Production Act of 1990,[148] USDA issued proposed rules that would have allowed characterizing a product as "organic" even if genetically engineered.[149] This provoked an outcry, leading the agency to issue a revised proposal a couple of years later that removed this controversial policy,[150] which became a final rule shortly thereafter.[151]

¶ 42 Consumer and environmental groups criticized the regulatory framework described in the 1992 policy statement, arguing that the FDA should use its food additive authority to require premarket notification, safety testing, and labeling disclosures for all bioengineered foods.[152] Even some biotech companies evidently have come to recognize the potential value of a more formal agency review process.[153] In 1999, the FDA showed signs that it might revisit many of these subjects by holding a series of public hearings around the country,[154] which led to the issuance of a proposed rule more than one year later.[155] Although consultations prior to marketing effectively became mandatory,[156] the

148. 7 U.S.C. §§ 6501-6518 (2000); *see also* Gordon G. Bones, *State and Federal Organic Food Certification Laws: Coming of Age?*, 68 N.D. L. REV. 405 (1992).

149. *See* National Organic Program, 62 Fed. Reg. 65,850 (1997) (proposing also to allow the use of irradiation in processing and sewage as fertilizer); *see also* Kenneth C. Amaditz, *The Organic Foods Production Act of 1990 and Its Impending Regulation: A Big Zero for Organic Food?*, 52 FOOD & DRUG L.J. 537 (1997).

150. *See* National Organic Program, 65 Fed. Reg. 13,512 (2000).

151. *See* National Organic Program Final Rule, 65 Fed. Reg. 80,548 (2000) (codified at 7 C.F.R. pt. 205). The regulations define genetic engineering as an "excluded method" for any organic foods. *See* 7 C.F.R. §§ 205.2, 205.105 (2006).

152. *See* Alliance for Bio-Integrity v. Shalala, 116 F. Supp. 2d 166 (D.D.C. 2000) (dismissing a challenge to the FDA's policy); GAO, NEW FOOD TECHNOLOGIES, *supra* note 104, at 45-48; McGarity, *supra* note 32, at 494-504, 509-10; Marion Burros, *Different Genes, Same Old Label*, N.Y. TIMES, Sept. 8, 1999, at F5.

153. *See Industry Presses FDA for Premarket Biotech Notification*, FOOD CHEM. NEWS, Dec. 5, 2002, at 5; Gillis, *supra* note 31, at E3 ("One proposal for tighter regulation of biotech crops was endorsed several years ago by virtually every group with a stake in the issue: the biotech industry, the food industry, environmentalists and consumer groups. The proposal was nearing approval as the Clinton administration left office, but the Bush administration has not acted on it."); *see also* Justin Gillis, *New Seed Planted in Genetic Flap*, WASH. POST, Feb. 6, 2000, at H1. Similarly, sponsors of biotech drugs now may benefit from having a less flexible but more certain regulatory environment. *See* Malinowski & O'Rourke, *supra* note 69, at 167-69, 246-48 (recommending the development of a stronger though still enlightened legal infrastructure to govern the commercialization of "genotechnologies").

154. *See* Marden, *supra* note 38, at 756-57.

155. *See* Premarket Notice Concerning Bioengineered Foods, 66 Fed. Reg. 4706 (2001) (to be codified at 21 C.F.R. pts. 192, 592) (proposing to require submission of a "pre-market biotechnology notice (PBN)"); *id*. at 4709 (anticipating "that the products of this technology are likely in some cases to present more complex safety and regulatory issues than seen to date"); Christine Cochran, Note, *Premarket Notice Concerning Bioengineered Foods: A Proposed Regulation Satisfying Some of the Players, Some of the Time*, 12 WASH. U. J.L. & POL'Y 173 (2003). Previously, FDA officials had expressed concerns that it lacked the statutory authority to create such a premarket notification system. *See* GAO, NEW FOOD TECHNOLOGIES, *supra* note 104, at 12.

156. Although not yet issued as a final rule, it may operate as a de facto requirement by virtue of the FDA's more general ability to pressure regulated firms to abide voluntarily. *See* Lars Noah, *Administrative Arm-Twisting in the Shadow of Congressional Delegations of Authority*, 1997 WIS. L. REV. 873, 876-98, 922-23; *see also* Gilhooley, *supra* note 141, at 1098 ("The agency has not issued a final rule, but the

subsequent transition from the Clinton to the Bush administration appears to have stalled whatever momentum existed at the agency.[157]

¶ 43 For the present, therefore, the agency continues to rely on an essentially case-by-case approach in determining whether to impose special requirements for GMOs.[158] Although flexibility in dealing with an emerging technology has obvious advantages, there is a case to be made for establishing clearer rules for bioengineered food products. The FDA's 1992 policy statement, with its emphasis on informal, ad hoc assessment, may perpetuate uncertainty for innovative companies and could weaken public confidence,[159] though recent surveys have found that most American consumers do not realize the prevalence of GMOs in the food supply.[160]

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voluntary cooperation of the industry is likely to lead to continued advance consultation with the agency."); Rockoff, *supra* note 37, at 4A.

157. The proposals do not even appear as "active" in the latest semi-annual regulatory agenda. *See* HHS, Unified Regulatory Agenda, 70 Fed. Reg. 26,818 (2005). Although these questions arose at the very outset of Clinton administration, the White House initially lacked clear direction on the subject. *See* Alex Barnum, *Biotech Poses Key Test for Clinton Administration: New Leadership Faces a Balancing Act Between the Environmental and High-Tech Sectors*, S.F. CHRON., Jan. 4, 1993, at B1.

158. *See* CONG. RESEARCH SERV., FOOD BIOTECHNOLOGY IN THE UNITED STATES: SCIENCE, REGULATION AND ISSUES (2001); Sophia Kolehmainen, *Precaution Before Profits: An Overview of Issues in Genetically Engineered Food and Crops*, 20 VA. ENVTL. L.J. 267 (2001); Sara J. MacLaughlin, *Food for the Twenty-First Century: An Analysis of Regulations for Genetically Engineered Food in the United States, Canada, and the European Union*, 14 IND. INT'L & COMP. L. REV. 375 (2003).

159. *See* McGarity, *supra* note 32, at 490 (suggesting that "the fragile veneer that has protected the regulatory process in the United States from overwhelming criticism is cracking," and referring to "the rapidly eroding level of public confidence in federal regulation of agricultural biotechnology"); *id*. at 473 ("The U.S. biotechnology industry entered the GM foods debates with an arrogance reminiscent of the nuclear power industry in the 1950s."); *id*. at 474 ("The condescending attitude of many federal officials has done little to inspire consumer confidence in the GM food economy."); Kurt Eichenwald, *Biotechnology Food: From the Lab to a Debacle*, N.Y. TIMES, Jan. 25, 2001, at A1 (harping on Monsanto's lobbying clout and supposed tactical blunders). One should not, however, exaggerate the extent to which the American public has lost faith in the food supply by virtue of the widespread use of GMOs. On the contrary, consumers seem to have lost whatever interest the question briefly sparked, at least until the next widely publicized scare, so this may amount to "much ado about nothing." Furthermore, if it presents an obstacle to successful commercialization of their products, firms will decide whether they would prefer stricter regulation as the price for maintaining this fragile public confidence. Finally, why does the purported squeamishness not extend to biotech drugs? Food differs, of course, and therapeutic agents offer substantial offsetting utilities (and face more comprehensive regulation), but patients are no more likely to understand the fact that a pharmaceutical manufacturer genetically engineered bacteria to produce a product. *See* Peter A. Singer & Abdallah S. Daar, *Avoiding Frankendrugs*, 18 NATURE BIOTECH. 1225 (2000).

160. *See* Linda A. Johnson, *Genetically Modified Foods More Common: And, Added a Survey, Most Americans Are Unaware They Have Been Eating Them for Years*, PHILA. INQUIRER, Mar. 24, 2005, at A8; *see also* Karen Hopkin, *The Risks on the Table*, SCI. AM., Apr. 2001, at 60 (noting that "an estimated 60 percent of processed foods in supermarkets – from breakfast cereals to soft drinks – contain a GM ingredient, especially soy, corn or canola"); Elizabeth Weise, *Americans Are Iffy on Genetically Modified Foods*, USA TODAY, Sept. 18, 2003, at 6D (reporting estimates that approximately three-quarters of all processed foods contain GM ingredients). Earlier surveys had indicated a lack of concern about – and a somewhat surprising willingness to accept potential risks from – GMOs more generally. *See* U.S. CONG., OFFICE OF TECH. ASSESSMENT, NEW DEVELOPMENTS IN BIOTECHNOLOGY: PUBLIC PERCEPTIONS OF BIOTECHNOLOGY 4 (1987); Thomas J. Hoban, *Consumer Acceptance of Biotechnology: An International Perspective*, 15 NATURE BIOTECH. 232 (1997); *cf*. Justin Gillis, *Shoppers Uneasy About Cloning: Poll Finds Worries over Meat and Milk*, WASH. POST, Nov. 16, 2005, at D1.

¶ 44 The negative European reaction to GM foods may help to underscore the point about the fragility of public confidence.[161] Although the EU recently began to authorize the sale of GM foods subject to labeling requirements and other restrictions,[162] the United States continues to press a formal complaint before the World Trade Organization (WTO).[163] One recent incident highlighted the continuing sensitivities about this issue. Over the course of several years, a biotech company inadvertently had sold seeds from a nearly identical but unapproved strain ("Bt10") of its approved pest-resistant GM corn ("Bt11").[164] USDA officials exacted fairly modest sanctions, but the EU decided to

161. *See* George Gaskel et al., *Worlds Apart? The Reception of Genetically Modified Foods in Europe and the U.S.*, 285 SCIENCE 384 (1999); Nigel Williams, *Agricultural Biotech Faces Backlash in Europe*, 281 SCIENCE 763 (1998); Lizette Alvarez, *Consumers in Europe Resist Gene-Altered Foods*, N.Y. TIMES, Feb. 11, 2003, at A3; William Hoge, *Britons Skirmish over Genetically Modified Crops*, N.Y. TIMES, Aug. 23, 1999, at A3 (describing protests); *see also* Marsha A. Echols, *Food Safety Regulation in the European Union and the United States: Different Cultures, Different Laws*, 4 COLUM. J. EUR. L. 525 (1998). In contrast, European regulators do not share the FDA's preoccupation with comprehensive premarket testing of pharmaceutical products (including those produced biotechnologically), placing far more effort into careful postmarket surveillance. *See* Evelyne Friedel & Michael Freundlich, *European Community Harmonization of the Licensing and Manufacturing of Medicinal Products*, 49 FOOD & DRUG L.J. 141, 168-70 (1994); Harvey Teff, *Drug Approval in England and the United States*, 33 AM. J. COMP. L. 567, 579 (1985); *see also* Teresa Pechulis Buono, Note, *Biotechnology-Derived Pharmaceuticals: Harmonizing Regional Regulations*, 18 SUFFOLK TRANSNAT'L L.J. 133 (1995).

162. *See* Joanne Scott, *European Regulation of GMOs and the WTO*, 9 COLUM. J. EUR. L. 213 (2003); Aaron A. Ostrovsky, Note, *The New Codex Alimentarius Commission Standard for Food Created with Modern Biotechnology: Implications for the EC GMO Framework's Compliance with the SPS Agreement*, 25 MICH. J. INT'L L. 813 (2004) (noting that it took the Codex committee seven years to develop risk assessment principles for GM foods). The EU first issued its policy on deliberate release of GMOs in 1990. *See* Council Directive 90/220/EEC, art. 8.5, 1990 O.J. (L 117) 15. After allowing the importation of GM soybean seed in 1996, *see* Commission Decision 96/281/EC, 1996 O.J. (L 107), the EU witnessed fierce public opposition that resulted in a de facto moratorium and the passage of more restrictive rules, *see* European Parliament & Council Directive 2001/18/EC, 2001 O.J. (L 106) (revising the 1990 Directive governing deliberate releases to require assessment of indirect risks, post-market surveillance, and a ten-year sunset on approvals); European Parliament & Council Regulation, 1829/2003, 2003 O.J. (L 268) (requiring tracking and labeling of GM foods). In 2004, after six years without authorizing the sale of any new GM foods, the EU approved Bt-11 corn. *See Monsanto Can Use a Gene-Modified Corn in Europe*, N.Y. TIMES, Oct. 27, 2004, at C4; *Monsanto Gets 10-Year EU License To Import Genetically Modified Corn*, PHILA. INQUIRER, Aug. 9, 2005, at C4.

163. *See* David Winickoff et al., *Adjudicating the GM Food Wars: Science, Risk, and Democracy in World Trade Law*, 30 YALE J. INT'L L. 81, 82-83, 86-90, 93, 118-21 (2005) (summarizing this dispute, and defending the EU's position because of the low certainty and lack of consensus about the risks associated with GM foods); Justin Gillis & Paul Blustein, *WTO Ruling Backs Biotech Crops: European Ban, Challenged by U.S. and Allies, Violates Trade Regulations, Panel Says*, WASH. POST, Feb. 8, 2006, at D1; Scott Miller & Juliane von Reppert-Bismarck, *Stricter Review Urged for Biotech Food*: *E.U. Agency May Rely More on Nations, Less on Firms*, WASH. POST, Apr. 13, 2006, at D5. Asian countries also have resisted importing GM foods. *See* Melody Petersen, *New Trade Threat for U.S. Farmers*, N.Y. TIMES, Aug. 29, 1999, § 1, at 1. Notwithstanding such objections, GMOs continue to make inroads on agriculture around the world. *See* Justin Gillis, *Bionic Growth for Biotech Crops: Gene-Altered Agriculture Trending Global*, WASH. POST, Jan. 12, 2006, at D1; Jehangir S. Pocha, *China May Lift Ban on Modified Rice*, BOSTON GLOBE, July 3, 2006, at E1.

164. *See* Michael S. Rosenwald, *Syngenta Says It Sold Wrong Biotech Corn*, WASH. POST, Mar. 23, 2005, at E1. In a similar incident, Monsanto alerted the FDA that some of its GM canola seed may have contained traces of another GM canola strain not yet reviewed for human use. *See* Scott Kilman, *Monsanto Admits Unapproved Seed May Be in Crops*, WALL ST. J., Apr. 15, 2002, at A3; *see also* Jill Carroll, *FDA*

impose a moratorium on essentially all imports of corn gluten from the United States.[165]

C. The Second Wave

¶ 45 During the first decade of widespread biotech commercialization, therapeutic products made the greatest impact while agricultural applications may have drawn the most public attention. In some respects, the biopharmaceutical industry now shows signs of retrenchment as it has matured, while agricultural biotech companies finally may see the unfulfilled possibilities of their work reach fruition. Indeed, with the growing prospect of molecular farming, the two sectors have begun to coalesce, and, as a consequence, the FDA continues to encounter new regulatory challenges.

1. Biotech Generics

¶ 46 As explained previously, biotechnology has generated some genuine therapeutic breakthroughs. These pharmaceutical advances have, however, not come cheaply. Whether because of the special difficulties in manufacturing these products or because of the narrow markets offered by orphan diseases (or some combination of these and perhaps other reasons), biotech drugs have triggered sticker shock for carrying annual price tags in the tens of thousands of dollars.[166] Medicare's tab just for EPO exceeds $1 billion annually. At the same time, several of the successful first generation biotech drugs have lost or soon will lose their patent protection and market exclusivity periods.

¶ 47 In the case of conventional pharmaceuticals, makers of generic copies already would have positioned themselves to enter the market, by virtue of special legislation enacted two decades ago that allowed clinical testing and conditional FDA approval pending expiration (or invalidation) of any remaining patent periods. To secure an abbreviated new drug approval (ANDA), the FDA only requires that the sponsor of a generic drug demonstrate that its product is "bioequivalent" to – meaning that it has essentially the same rate and extent of absorption as – the innovator drug, a showing that substitutes for the much costlier clinical trials demanded as part of an application for new drug approval (NDA) to demonstrate safety and effectiveness of the innovator drug.[167] Because manufacturers of generic drugs did not need to make the substantial investment

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Says Monsanto Canola Doesn't Appear To Pose Risks, WALL ST. J., Apr. 16, 2002, at B2 (reporting that the agency finessed this problem by construing the company's notification of the mistake as instead a request for premarket consultation).

165. *See* Raf Casert, *E.U. Votes Ban on U.S. Corn Gluten*, WASH. POST, Apr. 16, 2005, at E1 (reporting that U.S. officials called the EU's decision an "overreaction").

166. *See* Geeta Anand, *As Biotech Drug Prices Surge, US Is Hunting for a Solution*, WALL ST. J., Dec. 28, 2005, at A1; Alex Berenson, *Cancer Drugs Offer Hope, but at Huge Expense*, N.Y. TIMES, July 12, 2005, at A1 (reporting that Avastin can cost a colon cancer patient $54,000 per year and that Erbitux can run to $100,000 annually); *see also* Bernadette Tansey, *Genentech Profit Rockets 73%: Biotech Firm Sees Big Rise in Revenue from Cancer Drugs*, S.F. CHRON., July 12, 2005, at D1.

167. *See* 21 U.S.C. § 355(j)(2)(A)(iv) (2000); 21 C.F.R. pt. 320 (2006); Serono Labs., Inc. v. Shalala, 158 F.3d 1313, 1318-21 (D.C. Cir. 1998); Somerset Pharm., Inc. v. Shalala, 973 F. Supp. 443, 453-54 (D. Del. 1997) (deferring to the FDA's scientific judgment that metabolite testing could serve as an indicator of bioequivalence for generic versions of the drug selegiline hydrochloride indicated for the treatment of Parkinson's disease).

in drug discovery or premarket testing, they could sell their products at far less than the prices charged by the innovator company.

¶ 48 In the case of biotech drugs, however, the ANDA mechanism does not offer generic sellers the same ease of market entry. First, apart from those few products (i.e., insulin and growth hormone) approved as new drugs,[168] the FDA has used its biologics premarket review process for most biotech pharmaceutical products, which does not at present include the same statutory provisions governing approval of generic copies. Second, sponsors of "biogenerics" may find it impossible to satisfy the standard of proof normally required for ANDAs because large molecule drugs are derived through a complex and somewhat mysterious production process.[169] For this reason, innovator biotech firms have argued strenuously that generic competitors cannot establish bioequivalence.[170] Again, one might note some amount of hypocrisy insofar as these same companies have criticized the FDA's excessive preoccupation with licensing biologics manufacturing facilities, arguing that they now have enough precision in characterizing their end-products to ensure that production processes at different facilities will generate essentially identical agents.[171] These companies also embraced a more capacious notion of similarity, at least when hoping to block approvals of competing orphan drug products,[172] than they do after their period of market exclusivity expires and

168. *See* Philip D. Noguchi, *From Jim to Gene and Beyond: An Odyssey of Biologics Regulation*, 51 FOOD & DRUG L.J. 367, 368 (1996) (explaining that CDER exercised jurisdiction over these products because it previously had approved their non-biotech-derived counterparts as new drugs).

169. *See* Erika Jonietz, *Generic Biotech*, TECH. REV., Dec. 2004, at 54, 56 ("The reliance on living cells gives the process a black-box quality; small changes in, say, temperature or purification conditions can have unintended results, affecting how well a drug works or even causing severe side effects."); Marc Kaufman, *Biotech Drugs' Generic Future Debated*, WASH. POST, Feb. 10, 2005, at A1 (explaining that Centocor's Remicade® undergoes 310 discrete manufacturing steps); Michael Rosenwald, *Biotech Firm Gambles on New Plant: HGS Has Not Won Approval for Any Drug*, WASH. POST, Sept. 23, 2005, at D4.

170. *See* Anna Wilde Mathews & David P. Hamilton, *FDA Takes Step Toward Allowing Generic Versions of Biotech Drugs*, WALL ST. J., Feb. 18, 2004, at A1 ("Biotech companies argue that their medicines are too complex and prone to unexpected variations for others to duplicate them without performing the extensive tests conducted on the original products."); *cf.* Lars Noah, *Sham Petitioning as a Threat to the Integrity of the Regulatory Process*, 74 N.C. L. REV. 1, 5-11, 69-70 (1995) (describing the many ways that brand-name manufacturers of conventional drugs use submissions to regulatory agencies in an effort to exclude potential competitors); Leila Abboud, *Raging Hormones: How Drug Giant Keeps a Monopoly on 60-Year-Old Pill*, WALL ST. J., Sept. 9, 2004, at A1 (reporting that the long running battle to introduce a generic version of Premarin, which is derived from the urine of pregnant horses, "offers a preview of the looming debate" over biotech generics).

171. *See* Gamerman, *supra* note 31, at 226-34; *id*. at 221 ("New technologies enabled biologics manufacturers to purify and characterize their products to a degree which previously could be achieved only with pharmaceutical drugs."); *id*. at 226 ("The original scientific rationale for process-based regulation of biologics is not relevant to modern biologics . . . ."); Noah, *supra* note 9, at 749-50. The FDA partly accepted these arguments. *See* Elimination of Establishment Licensing Application for Specified Biotechnology and Specified Synthetic Biological Products, 61 Fed. Reg. 24,227 (1996) (codified at 21 C.F.R. § 601.2 (2006)); FDA's Policy Statement Concerning Cooperative Manufacturing Arrangements for Licensed Biologics, 57 Fed. Reg. 55,544 (1992); John Schwartz, *FDA Revises Biotechnology Rules*, WASH. POST, Nov. 13, 1995, at A19.

172. *See supra* notes 81-93 and accompanying text; *cf.* Bohrer & Prince, *supra* note 83, at 410-12 (noting an irony in the FDA's decision to approve an interferon beta drug based on clinical trials using a precursor compound while also concluding that this MS drug differed sufficiently from a previously approved orphan interferon beta drug).

generics become a threat.

¶ 49 In fact, after recently finding no deficiencies in an ANDA submission for a generic version of r-hGH, the FDA announced that it would have to delay further action on the application until it had an opportunity to resolve these sorts of fundamental regulatory and policy issues.[173] The technical question about bioequivalence may not pose an insurmountable obstacle for products that replace natural proteins in the body (e.g., EPO for treating anemia), though it may present an insuperable barrier for more complex products used to treat autoimmune diseases and cancer.

¶ 50 The FDA recently suggested use of an alternative mechanism for approving generic versions of early biotech drugs. Sometimes referred to as a "paper NDA," this route allows a company to bring a slightly modified version of a pioneer drug to market by cross-referencing the contents of the original NDA and filing supplemental research as deemed necessary.[174] This approach has triggered controversy because it essentially appropriates confidential safety and effectiveness data submitted by the sponsor of the innovator drug and may lead to FDA marketing approval even before the expiration of the patent term and exclusivity periods.[175] Congress ultimately may have to resolve the issue. Although biotech generics probably would not offer the same dramatic reductions in price seen with conventional drugs because of the need to invest in complex manufacturing facilities, they still promise substantial cost savings to patients and providers.

¶ 51 Public officials might take a broader lesson away from this debate. After beginning as underdogs in the pharmaceutical business that sometimes needed orphan drug protection to survive start-up,[176] the highly successful biotechnology firms now find themselves on the other side of the fence: well-established and battling against new entrants seeking to share in some of the profits. In short, one might say that at least some of the scrappy newcomers have become bullying incumbents. Unlike the medical device business, which generally sees lower sales volumes, greater decentralization, and incremental product development (and therefore intentionally remains subject to a

173. *See FDA Defers Approval of Novartis Growth Drug*, WALL ST. J., Sept. 3, 2004, at A8; *see also* David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD & DRUG L.J. 143 (2005); Stephen Heuser, *Regulators Struggle with Generic Biodrugs*, BOSTON GLOBE, Apr. 24, 2006, at E1 (reporting that the EU approved a generic version of this drug while FDA efforts to issue guidance have stalled).

174. *See* 21 U.S.C. § 355(b)(2) (2000); Jill D. Deal, *Some FDA Applications Can Escape Full Testing*, NAT'L L.J., May 22, 2000, at B18.

175. *See* Leila Abboud & Anna Wilde Mathews, *FDA To Allow Back Door for Some Generics*, WALL ST. J., Oct. 14, 2003, at B1; *see also* Scientific Considerations Related to Developing Follow-on Protein Products, 69 Fed. Reg. 50,386 (2004); *Hearing Before the Senate Judiciary Comm.: The Law of Biologic Medicine*, 108th Cong. (2004). The FDA continues to struggle with these issues. *See* Sandoz, Inc. v. Leavitt, 427 F. Supp. 2d 29 (D.D.C. 2006) (ordering the FDA to stop "egregious[ly]" delaying action on the generic r-hGH application); Diedtra Henderson, *FDA Clears a Generic Biotech Drug: Case Fails To Clarify the Approval Process*, BOSTON GLOBE, June 1, 2006, at D1.

176. *See supra* notes 81-93 and accompanying text; *see also* Burk, *supra* note 47, at 631 (summarizing the original profile of biotechnology firms as "small, entrepreneurial, research intensive, focused on a single product, having long lead times to market, and strongly tied to universities").

somewhat more lenient regulatory regime),[177] biopharmaceutical companies can and must shoulder the same burdens that the FDA has imposed on others in the drug industry. As a consequence, firms in this field embrace novelty (to reap the rewards that go with innovation) and resist efforts by competitors to free-ride by making use of a loose conception of substantial equivalence. In sharp contrast, in the case of agricultural applications of biotechnology, innovators receive no market exclusivity apart from the protections of patents and restrictive licensing arrangements,[178] and drawing attention to novelty can only attract unwanted scrutiny from regulatory officials, so firms embrace a broader conception of substantial equivalence in that domain.[179]

2. "Pharming"

¶ 52 After successfully bioengineering plants to serve agronomic purposes or to produce new and improved versions of raw agricultural commodities, scientists have begun pursuing the possibility of manufacturing entirely novel compounds by genetically engineering food crops.[180] Instead of using bioreactors (fermentation tanks) filled with engineered microorganisms to manufacture proteins and other drug substances, pharmaceutical companies could move some of their production process into the field – hence, the use of terms such as "pharming," "biopharming," or "molecular farming."[181] For instance, scientists have engineered corn plants to produce substances with therapeutic uses – in one case, gastric lipase, an enzyme used to treat digestive problems in patients with cystic fibrosis, and, in another case, trypsin, a protein used to make insulin. Other valuable industrial substances such as petrochemicals might be grown in a similar fashion. Indeed, given the importance of precision in the production of large molecule drugs and the seemingly inevitable variability seen in agricultural commodities

177. *See* Peter Barton Hutt et al., *The Standard of Evidence Required for Premarket Approval Under the Medical Device Amendments of 1976*, 47 FOOD & DRUG L.J. 605 (1992).

178. *See* Monsanto Co. v. McFarling, 363 F.3d 1336 (Fed. Cir. 2004); Mark D. Janis & Jay P. Kesan, *U.S. Plant Variety Protection: Sound and Fury . . . ?*, 39 HOUS. L. REV. 727, 776-77 (2002); Peter J. Goss, Comment, *Guiding the Hand That Feeds: Toward Socially Optimal Appropriability in Agricultural Biotechnology Innovation*, 84 CAL. L. REV. 1395, 1433 (1996) (concluding that "all currently available devices for protecting plant breeding innovations leave something to be desired"); *see also* Dan L. Burk, *DNA Rules: Legal and Conceptual Implications of Biological "Lock-Out" Systems*, 92 CAL. L. REV. 1553, 1557-59 (2004) (describing anti-germination and other genetic use restriction techniques as alternatives to licensing agreements).

179. A vaguely similar dynamic, with resulting differences in the quantity of information generated by suppliers, appears in the context of medical technologies and medical procedures. *See* Lars Noah, *Medicine's Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373, 447-49, 455 (2002).

180. *See* Anne Simon Moffat, *Toting up the Early Harvest of Transgenic Plants*, 282 SCIENCE 2176 (1998); Aaron Zitner, *Fields of Gene Factories*, L.A. TIMES, June 4, 2001, at A1. Conversely, food production might move indoors, as scientists engineer microorganisms to produce certain food stuffs in bioreactors and eliminate the need to harvest raw agricultural commodities. *See* Mark Sagoff, *Biotechnology and the Environment: Ethical and Cultural Considerations*, 19 ENVTL. L. REP. 10,520, 10,523 n.23 (1989).

181. *See* Glynis Giddings et al., *Transgenic Plants as Factories for Biopharmaceuticals*, 18 NATURE BIOTECH. 1151 (2000); Dan Ferber, *Something Funny Down on the Pharm*, POP. SCI., Apr. 2003, at 78, 80-81; Andrew Pollack, *New Ventures Aim To Put Farms in Vanguard of Drug Production*, N.Y. TIMES, May 14, 2000, § 1, at 1. In cyberspace, "pharming" refers to misdirecting Internet users to phony web pages in order to "harvest" their personal information.

caused by sometimes minor differences in growing conditions (e.g., soil, moisture, temperature, and light), non-pharmaceutical applications may have greater commercial plausibility in the short-term.[182]

¶ 53 The biggest objections to pharming focus, however, on the possible environmental impacts of "genetic pollution."[183] In contrast to the containment achieved with fermentation tanks and other industrial production processes, cultivation in the field would amount to a deliberate release. As with GM foods, opponents fear cross-pollination with native plants and food crops, which could imperil both people and wildlife,[184] or contamination of human food stuffs during distribution.[185] More vigorous GMOs could crowd out other species, or cross-pollination could make those species more susceptible to damage from pests and disease. In the event of contamination with plants engineered to produce human proteins, allergic reactions would represent the primary adverse effect, not any pharmacological activity (after all, large molecule drugs generally require injection because digestion breaks down the proteins). Nonetheless, fearing adverse public reaction to contamination cases, major food processors that had embraced biotechnology when it served agronomic purposes now have allied themselves with environmentalists and consumer activists in expressing opposition to pharming.[186]

¶ 54 Demands that pharming occur only in greenhouses or laboratories seem to be impractical, but the restrictions currently imposed by regulators, such as buffer zones,[187]

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182. *See* Zitner, *supra* note 180, at A1; *see also* Rebecca Dresser, *Ethical and Legal Issues in Patenting New Animal Life*, 28 JURIMETRICS J. 399, 409 n.70 (1988) ("One as yet unresolved question is whether molecular farming can yield [pharmaceutical] products pure enough to meet regulatory standards."); Paul Elias, *Tweaking Plants' Genes To Clean up Polluted Sites*, PHILA. INQUIRER, July 4, 2005, at C5 ("[D]umping engineered bugs on polluted sites has its dangers and drawbacks . . . , so researchers have turned to engineering plants to draw pollutants out of the ground.").

183. *See, e.g.*, Ctr. for Food Safety v. Veneman, 364 F. Supp. 2d 1202 (D. Haw. 2005) (rejecting USDA's motion to dismiss a challenge brought by public interest groups opposed to field testing); Rebecca M. Bratspies, *Consuming (F)ears of Corn: Public Health and Biopharming*, 30 AM. J.L. & MED. 371 (2004); Warren E. Leary, *Gene Inserted in Crop Plant Is Shown To Spread to Wild*, N.Y. TIMES, Mar. 7, 1996, at B14; Rick Weiss, *Gene-Altered Crops Denounced: Environmental Groups Seek Moratorium on Open-Air Tests*, WASH. POST, Aug. 16, 2006, at A3 (reporting that the judge in Hawaii ruled against the USDA on the merits).

184. *See, e.g.*, M.J. Wilkinson et al., *Hybridization Between* Brassica Napus *and* Brassica Rapa *on a National Scale in the United Kingdom*, 302 SCIENCE 401 (2003); *see also supra* note 134.

185. *See* Rowena C. Seto, *Selling the Pharm: The Risks, Benefits, and Regulation of Biopharmaceuticals*, 27 ENVIRONS 443, 454-58 (2004); *see also id*. at 464 (noting that APHIS has not performed any careful assessments of environmental risks); *id*. at 452-53, 465-66 (recognizing that pharming could result in significant cost savings, and concluding that these and other benefits outweigh the risks, which agencies should attempt to manage without inhibiting innovation).

186. *See* Scott Kilman, *Crops Bred To Produce Medicines Raise Contamination Worries*, WALL ST. J., Nov. 5, 2002, at B7 ("[P]olitically powerful trade groups for the $500 billion food sector are preparing to lobby federal regulators for new rules that would make life far more difficult for bio-pharming firms. . . . [Although] generally supportive of crop biotechnology thus far, . . . they don't want their favorite crops genetically modified for anyone else."); Stephanie Simon, *Fearing a Field of Genes: The Food Industry Loves Engineered Crops, but Not When Plants Altered To "Grow" Drugs and Chemicals Can Slip into Its Products*, L.A. TIMES, Dec. 23, 2002, at 1; Arlene Weintraub, *What's So Scary About Rice?: Biotech Crops Can Make Drugs – but They Must Be Kept out of the Food Chain*, BUS. WK., Aug. 1, 2005, at 58.

187. *See* Stanley H. Abramson & J. Thomas Carranto, *Genetically Engineered Agriculture: Crop Biotechnology: The Case for Product Stewardship*, 20 VA. ENVTL. L.J. 241 (2001).

cannot entirely prevent incidents of cross-pollination or contamination. In one recent incident, ProdiGene, Inc. arranged for farmers in the Midwest to grow small test plots of a type of corn engineered to produce a vaccine for pigs; the plots were to be surrounded by fields of soybeans, but the farmers failed to ensure that seed from the hybrid corn would not germinate in the field during the next growing season. In one plot, more than a hundred acres of surrounding corn fields had to be burned given the risk of cross-pollination, and, in the other plot, small amounts of the hybrid corn contaminated the harvested soybeans and required their destruction (a loss of approximately $3 million).[188] Unlike the StarLink™ episode, the potentially cross-pollinated crops and the contaminated harvest never entered the human food supply, but it did serve as a reminder that these risks are not entirely fanciful.[189]

¶ 55 In an effort to curb public fears and head off a regulatory response, the biotechnology industry recently adopted a voluntary moratorium on pharming anywhere near food crops.[190] Members of Congress have introduced bills to address the problem, and federal agencies have taken a more serious look at the issue.[191] For instance, the FDA issued a draft guidance that asserted, among other things, that it would apply GMP requirements to pharming operations,[192] and USDA has formulated amendments to its

188. *See Corn Near Gene-Altered Site To Be Destroyed*, N.Y. TIMES, Nov. 14, 2002, at C10; *see also* Justin Gillis, *EPA Fines Biotechs for Corn Violations*, WASH. POST, Dec. 13, 2002, at E3 (describing similar incidents involving other firms). It should be noted, however, that commingling with foreign substances of various types inevitably occurs during the harvesting, transportation, and storage of most crops.

189. Nor, evidently, did this represent an entirely isolated incident. *See* Andrew Pollack, *Modified Seeds Found Amid Unmodified Crops*, N.Y. TIMES, Feb. 24, 2004, at C6; Rick Weiss, *Next Food Fight Is Brewing over Listing Genes on Labels: Processors, Retailers Resisting Demand of Some Consumer Groups*, WASH. POST, Aug. 15, 1999, at A17 (describing Prima Terra's recall of thousands of bags of organic chips after it discovered that the corn supplied to it had been cross-pollinated by GM corn). More than a decade earlier, a GM rabies vaccine for cattle tested overseas may have affected farmworkers. *See* Philip J. Hilts & Bradley Graham, *Experimental Vaccine May Have Infected 17*, WASH. POST, Jan. 23, 1988, at A7.

190. *See* Justin Gillis, *Biotech Industry Adopts Precautions: Altered Plants Banned Near Major Food Crops*, WASH. POST, Oct. 22, 2002, at E1 (reporting that researchers also have begun to look at safflower and other alternatives to corn and canola to reduce the likelihood of cross-pollination); *see also* Paul Elias, *Forbidding Fruit?*, PHILA. INQUIRER, Jan. 28, 2006, at D1 (reporting that Hawaii has become a popular location for conducting field trials of GM crops). Scientists also have tried engineering corn plants to reduce the likelihood of cross-pollination or used non-food crops such as tobacco. *See* NAT'L RESEARCH COUNCIL, BIOLOGICAL CONFINEMENT OF GENETICALLY ENGINEERED ORGANISMS (2004); Justin Gillis, *Biotech Limits Found Lacking: Panel Calls for Controls on Genetic Engineering*, WASH. POST, Jan. 21, 2004, at E1. Another idea would use a firefly gene to make GM crops glow for easy identification. *See* Brian K. Harper et al., *Green Fluorescent Protein as a Marker for Expression of a Second Gene in Transgenic Plants*, 17 NATURE BIOTECH. 1125, 1128 (1999).

191. *See* Justin Gillis, *Farmers Grow a Field of Dilemma: Drug-Making Crops' Potential Hindered by Fear of Tainted Food*, WASH. POST, Dec. 23, 2002, at A1 (referring to efforts by USDA, FDA, and EPA, and noting that Senator Durbin had introduced a bill).

192. *See* Notice of Availability, Draft Guidance for Industry: Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals, 67 Fed. Reg. 57,828 (2002). In addition, investigational new drug (IND) rules could give the agency authority to restrict research and development involving pharmed therapeutic products.

rules governing field testing.[193]

¶ 56 Pharming represents the confluence of a pair of biotechnological advances – namely, the development of large molecule drugs and the capacity for modifying food crops – and no doubt magnifies the regulatory concerns that accompanied each of those earlier breakthroughs.[194] Although the FDA has dealt with combination products in the past,[195] harvesting therapeutic raw materials from a field introduces a whole new complexity. In effect, are the regulatory approaches to first-generation biotech products able to accommodate these latest innovations? Again, however, one needs to ask whether such concerns arise exclusively with pharming,[196] or whether they represent just the latest facet of broader concerns about the environmental impacts of intensive agricultural practices[197] or, for that matter, pharmaceutical manufacturing. In fact, only recently have scientists and regulators become aware of comparable environmental consequences

193. *See* Introduction of Plants Genetically Engineered To Produce Industrial Compounds, Interim Rule, 68 Fed. Reg. 46,434 (2003); Field Testing of Plants To Produce Pharmaceutical and Industrial Compounds, 68 Fed. Reg. 11,337 (2003); Andrew Pollack, *U.S. Imposes Stricter Rules for Genetically Modified Crops*, N.Y. TIMES, Mar. 7, 2003, at A23; *see also* Philip Brasher, *Biotech Corn Returns to Iowa*, DES MOINES REGISTER, June 11, 2005, at 1D (reporting that USDA approved two plots on a fenced Army base more than a mile from the nearest corn crop and subject to other restrictions).

194. *See* Mandel, *supra* note 32, at 2258-59 ("Next-generation biotechnological advances are fast-approaching . . . . The risks to human health and the environment presented by [these advances] . . . will include risks of different types than those posed by transgenic products to date. . . . [I]t is imperative that the statutory and regulatory structures be properly revised to provide for the effective and efficient regulation of genetically modified products.").

195. Recognizing that some technologies would not fit neatly into just one of the existing definitions, Congress amended the statue in 1990 to provide, among other things, that a "combination product" should be regulated according to its "primary mode of action." 21 U.S.C. § 353 (2000); *see also* 21 C.F.R. § 3.2 (2006).

196. In fact, non-GM crops have presented problems with cross-pollination and cross-contamination, as with canola and its natural progenitor rapeseed, which produces oil for industrial uses that can be toxic if accidentally consumed. *See* Richard Lorant, *Mass Poisoning in Spain Still Steeped in Mystery*, L.A. TIMES, June 16, 1991, at A6.

197. *See, e.g.*, Warren A. Braunig, Note, *Reflexive Law Solutions for Factory Farm Pollution*, 80 N.Y.U. L. REV. 1505 (2005); Susan M. Brehm, Comment, *From Red Barn to Facility: Changing Environmental Liability To Fit the Changing Structure of Livestock Production*, 93 CAL. L. REV. 797 (2005); Juliet Eilperin, *In California, Agriculture Takes Center Stage in Pollution Debate*, WASH. POST, Sept. 26, 2005, at A1. Intensive agricultural practices involving livestock (such as crowding, the indiscriminate use of antibiotics, and feeding recycled high protein diets) also pose direct human health risks, as revealed by scares involving "mad cow disease" in England and avian flu emerging in Asian countries. *See* Thomas O. McGarity, *Federal Regulation of Mad Cow Disease Risks*, 57 ADMIN. L. REV. 289 (2005); David Brown, *Scientists Race To Head Off Lethal Potential of Avian Flu*, WASH. POST, Aug. 23, 2005, at A1. On the adverse consequences of overusing antibiotics in livestock, see Barbara O'Brien, *Animal Welfare Reform and the Magic Bullet: The Use and Abuse of Subtherapeutic Doses of Antibiotics in Livestock*, 67 U. COLO. L. REV. 407 (1996); Vincent Perreten et al., *Antibiotic Resistance Spread in Food*, 389 NATURE 801 (1997). Another common refrain emphasizes that biotech risks differ because GMOs propagate while other pollutants disperse, creating a greater risk of irreversibility in the case of the former threat to the environment. This view disregards the problems with bioaccumulation of conventional pollutants (increased pollutant concentrations as one moves up a food chain), to say nothing of the largely irreversible consequences of their persistence. *See* Brad Knickerbocker, *Toxic Releases Decline, but Worst Soups Persist*, CHRISTIAN SCI. MONITOR, May 17, 2005, at 2 (discussing EPA concerns about so-called "persistent bioaccumulative toxic chemicals," which include dioxin, mercury and PCBs); *see also* Juliet Eilperin, *Harmful Teflon Chemical To Be Eliminated by 2015*, WASH. POST, Jan. 26, 2006, at A1.

associated with the production and use of conventional drugs, particularly the risk of water pollution.[198] Similarly, rapid innovations in computer technology and consumer electronics such as cell phones have resulted in the disposal of large numbers of obsolete products in landfills where lead and other heavy metals might leach into groundwater.[199]

3. Transgenic Beasts

¶ 57 Genetically modified animals, whether engineered for food use or pharmaceutical production, pose related concerns.[200] It should be noted, however, that, as in the case of agricultural crops, traditional breeding efforts sometimes have taken familiar livestock far afield from their natural progenitors,[201] to say nothing of the unnatural inputs that have become common features of intensive agricultural practices.[202] Even so, in contrast to

198. *See* Juliet Eilperin, *Pharmaceuticals in Waterways Raise Concern*, WASH. POST, June 23, 2005, at A3. Researchers have discovered several active drug substances – including hormones, antibiotics, analgesics, and chemotherapy agents – in surface and ground water at measurable and potentially hazardous concentrations. *See* Dana W. Kolpin et al., *Pharmaceuticals, Hormones and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance*, 36 ENVTL. SCI. & TECH. 1202 (2002); Christopher T. Nidel, *Regulating the Fate of Pharmaceutical Drugs: A New Prescription for the Environment*, 58 FOOD & DRUG L.J. 81, 81-90, 101 (2003) (summarizing this research, and arguing that the FDA should take its responsibilities under NEPA more seriously when approving new drugs); Andrew C. Revkin, *F.D.A. Considers New Tests for Environmental Effects*, N.Y. TIMES, Mar. 14, 2002, at A20.

199. *See* Rachel Conrad, *Gadget Garbage: The Biggest Problems Are Created by the Smallest Devices*, MIAMI HERALD, Apr. 22, 2005, at C1 (discussing the growing problem of "e-waste"); *see also* Betsy M. Billinghurst, Note, *E-Waste: A Comparative Analysis of Current and Contemplated Management Efforts by the European Union and the United States*, 16 COLO. J. INT'L ENVTL. L. & POL'Y 399 (2005).

200. *See* NAT'L RESEARCH COUNCIL, ANIMAL BIOTECHNOLOGY: SCIENCE-BASED CONCERNS (2002) (recommending a mandatory approval system for transgenic animals); PEW INITIATIVE ON FOOD & BIOTECHNOLOGY, BUGS IN THE SYSTEM?: ISSUES IN THE SCIENCE AND REGULATION OF GENETICALLY MODIFIED INSECTS (2004); Carol Lewis, *A New Kind of Fish Story: The Coming of Biotech Animals*, FDA CONSUMER, Jan.-Feb. 2001, at 4; Anne S. Moffat, *Transgenic Animals May Be Down on the Pharm*, 254 SCIENCE 35 (1991). For instance, an accidental release already has occurred. *See* Andrew Pollack, *F.D.A. Says Food Supply May Contain Altered Pigs*, N.Y. TIMES, Feb. 6, 2003, at A26.

201. *See* Marian Burros, *The Hunt for a Truly Grand Turkey, One That Nature Built*, N.Y. TIMES, Nov. 21, 2001, at F1; *see also* Simon Crompton, *Pull the Udder One*, LONDON TIMES, May 20, 2003, § 2, at 11 (discussing suspicions that intensively bred dairy cattle produce a type of milk protein that may trigger diabetes). Spontaneous gene mutations may turn benign naturally-occurring organisms into pests or disease vectors. *See* Scott D. Deatherage, *Scientific Uncertainty in Regulating Deliberate Release of Genetically Engineered Organisms: Substantive Judicial Review and Institutional Alternatives*, 11 HARV. ENVTL. L. REV. 203, 207-08 (1987) (drawing a different lesson from these illustrations).

202. *See supra* note 197. Furthermore, negative impacts on the ecosystem may arise with conventional cross-breeding, as happened, for instance, with the "Africanized" honeybee. *See* Jan Hollingsworth, *Africanized Honeybee Swarms Sought*, TAMPA TRIB., Jan. 31, 2003, at 1. A scientist imported the gypsy moth more than a century ago in hopes of cross-breeding this pest with the commercially valuable silkworm. *See* David Manspeizer, Note, *The Cheshire Cat, the March Hare, and the Harvard Mouse: Animal Patents Open up a New, Genetically-Engineered Wonderland*, 43 RUTGERS L. REV. 417, 431-32 (1991); *see also* Juliet Eilperin, *It Sprouts! It Climbs! It Strikes Without Warning!*, WASH. POST, July 25, 2005, at A7 (reporting one estimate that "there are 50,000 plants and animals that came from somewhere else, costing the United States more than $125 billion a year"). According to a still-circulating story (evidently propagated at least in part by persons affiliated with Florida State University), the lovebugs that have become the bane of drivers in the southeastern United States emerged from a botched experiment at the University of Florida. *See* Erik Maza, *Story Sticks with UF Like a Lovebug to a Bumper*, GAINESVILLE SUN, May 17, 2005, at B2; Lisa Thomas, *Love These Bugs? Only an Entomologist*

the voluntary and informal process it has used for transgenic plants, the FDA has decided to regulate GM livestock using it authority over "animal drugs" (on the theory that the introduced genetic material and expressed protein affect the animal's "structure or function" in much the same manner as conventional veterinary drugs might do),[203] demanding proof of safety, at least when these qualify as "new" animal drugs used in species intended for consumption by humans.[204] In one of the first applications it has received, Aqua Bounty Farms, Inc. requested approval to sell a transgenic Atlantic salmon designed to produce growth hormone year round so that the fish attain greater size, more quickly and producing less waste.[205] A few states, however, already have prohibited the sale of GM fish.[206]

¶ 58 Transgenic animals incorporating human genes raise still additional worries. Scientists may develop such hybrids in order to create closer models of human diseases in

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Could, GAINESVILLE SUN, May 27, 2005, at B3. My colleagues across campus have assured me that absolutely no basis exists for this urban legend.

203. *See* Graham M. Wilson, Note, A *Day on the Fish Farm: FDA and the Regulation of Aquaculture*, 23 VA. ENVTL. L.J. 351, 376 (2004) ("Although the FDA has not published any formal policy on the regulation of transgenic animals, indications from numerous publications signal that genetic modifications inserted into animals will be treated as drugs."); *id*. at 378 ("[T]he NADA [new animal drug approval] process, with its safety, effectiveness and limited environmental impact requirements, may provide adequate pre-market review to evaluate most concerns regarding genetically modified animals. . . . [These will] undergo a much more intensive screening process than comparable genetically engineered changes to plants."). The agency first officially took this position in 1986 in connection with the publication of the Coordinated Framework. *See* 51 Fed. Reg. at 23,304.

204. *See* 21 U.S.C. § 360b (2000); 21 C.F.R. pt. 514 (2006); *cf.* Justin Gillis, *Clone-Generated Milk, Meat May Be Approved: Favorable FDA Ruling Seen as Imminent*, WASH. POST, Oct. 6, 2005, at A1. USDA's Food Safety and Inspection Service (FSIS) also would have primary authority over meat derived from such livestock. Notably, the FDA does not have any jurisdiction over animal "biologics," which the USDA controls under the Virus-Serum-Toxin Act of 1913 (VSTA). *See* 21 U.S.C. §§ 151-159 (2000); 9 C.F.R. § 101.2(w) (2006); Grand Labs., Inc. v. Harris, 660 F.2d 1288, 1292 (8th Cir. 1981) (concluding that Congress intended "to leave the regulation of animal biologics shipped across state lines in the Department of Agriculture, where it had been since 1913"); *see also* Daniel D. Jones, *Genetic Engineering in Domestic Food Animals: Legal and Regulatory Considerations*, 38 FOOD DRUG COSM. L.J. 273, 283-86 (1983); William H. von Oehsen, III, *The FDA's Regulation of Veterinary Biotechnology: Business as Usual or a New Era of Environmental Protection*, 43 FOOD DRUG COSM. L.J. 847 (1988); *cf.* 21 C.F.R. §§ 510.4, 511.1(b)(5) (2006) (exempting animal biologics from NADA requirements only if they fully comply with VSTA); Terry L. Medley, *Issues in Assessing the Environmental Impact of Veterinary Biologics Produced Through Biotechnology*, 43 FOOD DRUG COSM. L.J. 821 (1988).

205. *See* Dorothy W. Bisbee, *Preparing for a Blue Revolution: Regulating the Environmental Release of Transgenic Fish*, 12 VA. ENVTL. L.J. 625 (1993); Robert H. Devlin et al., *Growth of Domesticated Transgenic Fish*, 409 NATURE 781 (2001); Tony Reichhardt, *Will Souped up Salmon Sink or Swim?*, 406 NATURE 10 (2000); Erik Stokstad, *Engineered Fish: Friend or Foe of the Environment*, 297 SCIENCE 1797 (2002); Janye Kay, *"Frankenfish," Spawn Controversy: Debate over Genetically Altered Salmon*, S.F. CHRON., Apr. 29, 2002, at A4; *see also* Wilson, *supra* note 203, at 378-84; *id*. at 381 ("[T]he greatest environmental concern regarding transgenic fish is that they will be released into the open ocean and disrupt the natural ecosystem."); *id*. at 383 (suggesting that FDA condition approval on a requirement "that transgenic salmon be raised in land-locked facilities"); *id*. at 387-94 (discussing labeling issues). Both USDA and EPA concluded, however, that they did not enjoy regulatory jurisdiction over the GM salmon.

206. *See* MD. CODE ANN. § 4-11A-02 (2000); MICH. COMP. LAWS ANN. §§ 286.874(9), 324.41301-.41309 (West Supp. 2005); OR. ADMIN. R. 635-007-0595 (2005); WASH. ADMIN. CODE § 220-76-100 (2005).

laboratory animals for research purposes,[207] to engineer livestock capable of producing human proteins such as insulin or clotting factors needed by hemophiliacs,[208] and to produce closer tissue matches for organs harvested from animals for transplantation into humans (so-called "xenotransplants").[209] Although scientists have made "humanized" animals for some time, questions have begun to arise about the point where more substantial transfers of human genes might cross the line and create a part-human organism (sometimes designated as a "chimera").[210] For instance, at what point do the more stringent federal guidelines for human research subjects trump the more lenient protections governing laboratory animals?[211] In addition, when does the non-patentability of human organisms trump the patentability of genetically engineered animals? The Patent and Trademark Office recently rejected an application for a technique that purportedly blended embryonic cells from a human and a primate.[212] Closer questions may arise when scientists introduce human stem cells into a developing animal fetus (which ensures that purely animal germ cells have developed already), especially if these ultimately will develop into brain cells.[213]

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207. *See* Elan Pharm., Inc. v. Mayo Found. Med. Educ. & Research, 346 F.3d 1051 (Fed. Cir. 2003) (en banc); Carrie F. Walter, Note, *Beyond the Harvard Mouse: Current Patent Practice and the Necessity of Clear Guidelines in Biotechnology Patent Law*, 73 IND. L.J. 1025, 1029-31 (1998); Paul Elias, *Mighty Mice Help Scientists Find Cures*, PHILA. INQUIRER, Aug. 8, 2005, at E3.

208. *See* Infigen v. Advanced Cell Tech., Inc., 65 F. Supp. 2d 967 (W.D. Wis. 1999); Stephen Heuser, *GTC Gets Surprise Boost from EU*, BOSTON GLOBE, June 3, 2006, at F7 (reporting that GTC Biotherapeutics plans to apply for FDA approval to market Atryn, an anticlotting protein derived from the milk of genetically engineered goats, which, if successful, would make it the first commercial application of this approach for producing human pharmaceuticals); Lisa Krieger, *Implanted Gene Can Be Passed from Hen to Egg: Procedure Could Lead to Feathered Medicine Factories*, HOUS. CHRON., June 8, 2006, at A16.

209. *See* Martha Groves, *Transgenic Livestock May Become Biotech's Cash Cow: New Drugs and Organs for Treatment Are Among Goals, but Obstacles – Including Potential Backlash – Are Plentiful*, L.A. TIMES, May 1, 1997, at A1; Rick Weiss, *Gene Alteration Boosts Pig-Human Transplant Feasibility*, WASH. POST, Jan. 4, 2002, at A11. For instance, by adding certain human stem cells to developing sheep fetuses, the animals grow livers that closely resemble a human liver. The agency has issued a few guidance documents on the use of transgenic animals for organ harvesting and transplantation into humans. *See, e.g.*, Notice of Availability, PHS Guideline on Infectious Disease Issues in Xenotransplantation, 66 Fed. Reg. 8120 (2001); *see also* Jodi K. Frederickson, *He's All Heart . . . and a Little Pig Too: A Look at the FDA Draft Xenotransplant Guideline*, 52 FOOD & DRUG L.J. 429 (1997); Jack M. Kress, *Xenotransplantation: Ethics and Economics*, 53 FOOD & DRUG L.J. 353 (1998).

210. *See, e.g.*, D. Scott Bennett, Comment, *Chimera and the Continuum of Humanity: Erasing the Line of Constitutional Personhood*, 55 EMORY L.J. 347 (2006); Nicole E. Kopinski, Note, *Human-Nonhuman Chimeras: A Regulatory Proposal on the Blurring of Species Lines*, 45 B.C. L. REV. 619 (2004).

211. *See* Rick Weiss, *Of Mice, Men and In-Between: Scientists Debate Blending of Human, Animal Forms*, WASH. POST, Nov. 20, 2004, at A1.

212. *See* Rick Weiss, *U.S. Denies Patent for a Too-Human Hybrid*, WASH. POST, Feb. 13, 2005, at A3 (explaining that the PTO had issued patents for bacteria, yeast, and more than 400 modified animals, but had a longstanding policy against patenting human organisms, and adding that this issue "put[s] the patent office in an awkward position of being the federal arbiter of what is human"); *see also* Pub. L. No. 109-108, § 623, 119 Stat. 2290, 2342 (2005) ("None of the funds appropriated or otherwise made available under this Act may be used to issue patents on claims directed to or encompassing a human organism."); Dan L. Burk, *Patenting Transgenic Human Embryos: A Nonuse Cost Perspective*, 30 HOUS. L. REV. 1597 (1993); Esther Slater McDonald, *Patenting Human Life and the Rebirth of the Thirteenth Amendment*, 78 NOTRE DAME L. REV. 1359 (2003).

213. *See* Mark Greene et al., *Moral Issues of Human/Non-Human Primate Neural Grafting*, 309 SCIENCE 385 (2005); Rick Weiss, *Human Brain Cells Are Grown in Mice: Success Is Encouraging for*

D. Frivolous and Malevolent Applications

¶ 59 Although biotechnology has made its biggest splash in the pharmaceutical and agricultural arenas, it also has turned up in some unlikely and disturbing places. First, the genetic engineering of animals has begun to move from the farm to the home, presenting curious though fairly trivial questions about the exercise of existing regulatory authority. Second and far more troubling, though so far still speculative, the relative ease of modifying microorganisms has raised the specter of even more powerful biowarfare agents in the future.

1. Household Flora and Fauna

¶ 60 Transgenics have entered the pet trade: freshwater aquarium enthusiasts now can purchase the "GloFish," zebra danios with a gene inserted from sea anemone or coral, which gives them a red glow that becomes luminescent under black light.[214] Although the inventors originally had designed the GloFish as a way of detecting water pollution, detractors now complain about the frivolous use of the fish, while defenders argue that the modifications do not differ fundamentally from the long history of selective breeding of dogs and other pets.[215] In 2003, the FDA announced that it found no reason to subject the GloFish to premarket review as a new animal drug,[216] though California officials have blocked its sale.[217] In light of plans to bioengineer other companion animals (e.g., dander-free cats) as well as clone beloved pets, activists have petitioned the USDA to assert regulatory jurisdiction.[218]

Stem Cell Therapies, WASH. POST, Dec. 13, 2005, at A3; Rick Weiss, *Stem Cell Guidelines Issued*, WASH. POST, Apr. 27, 2005, at A2 ("Injection of human embryonic cells into monkey or ape embryos to make primate chimeras would be banned [under new guidelines recommended by the National Academy of Sciences], as would the creation of any human-animal chimera in which a human-like brain would be likely to develop."); *id*. ("Any chimeras that have the biological potential to make human sperm or eggs should not be allowed to breed, the report adds, to prevent creation of a human embryo in an animal's womb.").

214. *See* Griff Witte, *Shining Under Scrutiny: New Biotech Pets Make Some Uneasy*, WASH. POST, Mar. 13, 2004, at A1.

215. *See id*.

216. *See* Int'l Ctr. for Tech. Assessment v. Thompson, 421 F. Supp. 2d 1 (D.D.C. 2006) (rejecting a challenge to the agency's decision); *see also* Rekha K. Rao, Comment, *Mutating Nemo: Assessing the Environmental Risks and Proposing the Regulation of the Transgenic GloFish®*, 57 ADMIN. L. REV. 903 (2005); Andrew Pollack, *So, the Fish Glow, but Will They Sell?*, N.Y. TIMES, Jan. 25, 2004, § 3, at 5 (adding that the fish will come in other colors in the future). The agency long ago restricted the pet trade in small fresh water turtles, though under its authority to prevent sales of items that transmit communicable diseases (in this case, salmonella). *See* Louisiana v. Mathews, 427 F. Supp. 174 (E.D. La. 1977); Denise Grady, *Tiny Pet Turtles Return: Salmonella Does, Too*, N.Y. TIMES, Mar. 15, 2005, at F9.

217. *See* Antonio Regalado, *Pet Cloning Sparks Backlash*, WALL ST. J., Feb. 10, 2005, at D6 (adding that a bill to ban the sale of cloned or genetically engineered pets has been introduced by one state legislator); *see also* CAL. CODE REGS. tit. 14, § 671 (2005). Cloning may offer a method for preserving animal species nearing extinction. *See* Jeremy Manier, *Dying Breeds May Get Cloning Lifeline*, CHI. TRIB., Apr. 8, 2003, at C1.

218. *See* Rick Weiss, *Pet Clones Spur Call for Limits*, WASH. POST, Feb. 17, 2005, at A3 (reporting that the American Anti-Vivisection Society "petitioned the Agriculture Department to regulate pet-cloning companies as it does other animal research labs under the Animal Welfare Act"); *see also* Rick Weiss, *In a Furry First, a Dog Is Cloned in South Korea*, WASH. POST, Aug. 4, 2005, at A1 (noting that this organization "recently failed to force the [FDA] to regulate pet cloning"). For more on the fairly limited

¶ 61 In a recent article, Rebecca Bratspies provided a detailed and extremely critical account of the FDA's handling of the GloFish case.[219] Her thesis suffers, however, from numerous shortcomings, which in some sense typifies far too much of the existing legal scholarship on issues related to biotechnology. Among other things, she contends that "[t]he GRAS process is very specific – little is left to agency discretion."[220] Nothing

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scope of this statute, which excludes farm animals and lab rats from coverage, see Carole Lynn Nowicki, *The Animal Welfare Act: All Bark and No Bite*, 23 SETON HALL LEGIS. J. 443, 466 (1999).

219. *See* Rebecca M. Bratspies, *Glowing in the Dark: How America's First Transgenic Animal Escaped Regulation*, 6 MINN. J.L. SCI. & TECH. 457 (2005). Although she selects a quote from Dr. Seuss as an epigram, *see id*. at 457 ("One fish, two fish, red fish, blue fish, ..."), the classic children's story of Chicken Little – who repeatedly expresses fear that "the sky is falling" after getting hit on the head by an acorn – would have made more sense given her decidedly overheated rhetoric. *See, e.g.*, *id*. at 460 (calling the agency's decision "momentous" and a "watershed event"); *id.* at 470 (warning of potentially "devastating" consequences); *id*. at 471 ("In light of these high stakes, the relaxed, even inattentive, regulatory scrutiny the FDA applied to GloFish appears wildly inappropriate."); *id*. at 482 (complaining that the FDA has "unleashed" the GloFish into commercial distribution); *id*. at 485 (objecting that the agency has let loose "a transgenic, highly mobile organism with no consideration of the likely environmental effects," which might include "significant ecological effects"). Who could have imagined that the FDA's decision on this little fish might have such dire consequences (or that this purportedly peer-reviewed journal would accept such work)?! Her discussion of the GM salmon, *see id*. at 493-502, makes a great deal more sense, but the FDA has subjected Aqua Bounty's NADA application to full premarket review, *see supra* note 203. Once again, however, her repeated suggestions that the agency will do an inadequate job of assessing the environmental impacts in no way distinguishes this product from non-GM new animal drugs – for instance, one can imagine a conventionally produced antibiotic intended for use in fish to facilitate more intensive aquaculture practices. *Cf.* U.S. Public Interest Research Group v. Atlantic Salmon of Maine, LLC, 257 F. Supp. 2d 407, 434 (D. Me. 2003) (granting an injunction against the stocking of conventionally bred salmon); Gilhooley, *supra* note 141, at 1118 (conceding that non-GM farm-raised salmon differ from their free-range cousins in a variety of ways); Juliet Eilperin, *White House Seeks To Boost Fish Farms by Expanding into Open Waters*, WASH. POST, June 8, 2005, at A7 (reporting that the Bush administration "want[s] to quintuple domestic fish farming by 2025"). Perhaps the FDA does need to pay closer attention to secondary effects (as it did in reviewing rBST, *see supra* notes 144-46 and accompanying text), but this would be equally true of GM and non-GM new animal drugs.

220. Bratspies, *supra* note 219, at 489; *see also id.* at 476 ("Nor can GloFish qualify under the statute's definition of GRAS."); *id*. at 478 ("Under the plain language of the statute, GloFish therefore cannot be considered GRAS."). These and other emphatic conclusions, *see, e.g.*, *id*. at 476 ("GloFish clearly qualify as an adulterated product under this standard."), flow from a simplistic (overly literal and un-nuanced) application of the hardly plain language of the statute, and they fly in the face of the way regulatory agencies operate in practice and the extent to which reviewing courts defer. If GRAS applies (based on what she regards as an overbroad notion of substantial equivalence), then this arguable "animal drug" simply does not count as a "new" one (as these statutory terms of art operate), and her allegations that the agency has failed to enforce NADA requirements, *see, e.g.*, *id*. at 488-90, become *non sequiturs*. Finally, Ms. Bratspies also notes that the FDA never expressly invoked the GRAS exception, *see id*. at 478, but this reflects a decidedly cramped reading of the agency's admittedly cryptic announcement. As suggested previously, the FDA's ruling on Calgene's FLAVR SAVR tomato petition amounted to only an implicit GRAS affirmation. *See supra* note 103 and accompanying text. Prompted by its tentative review of this first GM food, the FDA issued a policy statement that more explicitly invoked GRAS principles. *See supra* notes 120-22 and accompanying text. When they lack confidence in their position, agencies are not above engaging in some intentional obfuscation. *See, e.g.*, Noah, *supra* note 50, at 651-52 (noting that the FDA has never fully explained the basis for its remarkable claim to jurisdiction over human cloning); Noah, *supra* note 156, at 877-78 nn.10-11, 887-91 & n.66 (discussing agency "jawboning" and "raised eyebrow" techniques).

could be further from the truth.[221] If, in the future, the FDA had a change of heart and decided to treat the GloFish as an unapproved and therefore adulterated new animal drug, a court undoubtedly would sustain the agency's conclusion that the product no longer qualified as GRAS,[222] but, where the FDA has concluded otherwise, an objecting party would have a difficult time persuading a court to disagree and force the agency's regulatory hand.[223] Second, and in a related vein, Ms. Bratspies argues that the FDA has inverted the burden of proof in contravention of statute and left the GloFish completely unregulated.[224] This is simply inaccurate.[225]

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221. *See* Noah & Merrill, *supra* note 49, at 349-64, 377-81, 440-43; *id*. at 441 (concluding that "the breadth of the GRAS exception provides industry the unusual opportunity to 'reform' the [food additive] approval process unilaterally"). For instance, the creative use of GRAS principles allowed the FDA to address over-the-counter (OTC) human drugs more efficiently on a category-wide basis. *See* Patrick R. Jones, Note, *Protecting the Consumer from Getting Burned: The FDA, the Administrative Process, and the Tentative Final Monograph on Over-the-Counter Sunscreens*, 20 AM. J.L. & MED. 317 (1994); David Selmer, Note, *The FDA's Over-the-Counter Drug Review: Expeditious Enforcement by Rulemaking*, 11 U. MICH. J.L. REFORM 142 (1977). The agency presumably could do something similar in the case of transgenic aquarium fish or other non-food critters. Indeed, the FDA's implementing regulations already contemplate simplified NADA reviews for "minor use applications," defined to include use in animals other than mammals or fowl. *See* 21 C.F.R. § 514.1(d) (2006). *But cf.* Mark Klock, *A Modest Proposal To Rename the FDA: Apologists for Carcinogens, Teratogens, and Adulterated Drugs*, 36 ARIZ. ST. L.J. 1161 (2004) (lambasting the agency for its failure to regulate drugs used with ornamental fish).

222. *Cf.* Alliance for Bio-Integrity v. Shalala, 116 F. Supp. 2d 166 (D.D.C. 2000) (conceding that in the future the agency could announce that GM food was materially different from conventional food). The three decisions that she cites all represented enforcement actions brought by the government. *See* Bratspies, *supra* note 219, at 478 nn.91-94. Although the FDA can demand "substantial evidence" in the form of controlled studies published in the scientific literature and refuse to consider anecdotal reports offered in support of a claim to GRAS status, *see id*. at 478, ultimately "safe" is not a matter of proof so much as it represents a judgment call based on all available evidence and appropriate inferences, *cf*. Lars Noah, *Scientific "Republicanism": Expert Peer Review and the Quest for Regulatory Deliberation*, 49 EMORY L.J. 1033, 1072-73, 1076-78 (2000); Ruth E. Harlow, Note, *The EPA and Biotechnology Regulation: Coping with Scientific Uncertainty*, 95 YALE L.J. 553, 560-63 (1986). In other words, if you have a "no brainer" (e.g., if the question got framed solely in terms of the safety and effectiveness of the genetic modification to the animal), then the agency need not insist on evidence drawn from rigorous peer-reviewed research.

223. *See, e.g.*, Schering Corp. v. Heckler, 779 F.2d 683 (D.C. Cir. 1985); *see also* Simpson v. Young, 854 F.2d 1429, 1435 (D.C. Cir. 1988) (rejecting a third party's effort to insist that the FDA hold an applicant to follow a guideline). In addition to new animal drugs, the GRAS exception appears in the definitions of "new drug" and "food additive." *See* 21 U.S.C. §§ 321(p)(1), 321(s) (2000). A survey of the case law involving challenges to FDA decisions to invoke the exception reveals significant judicial deference and occasional remands based on issues other than the factual and policy judgment concerning GRAS status. *See* LARS NOAH, LAW, MEDICINE, AND MEDICAL TECHNOLOGY Ch. 1(B)(4) (2d ed. forthcoming Dec. 2006).

224. *See* Bratspies, *supra* note 219, at 459 ("Th[e] announcement that the FDA would not to [sic] regulate GloFish meant that no federal agency was exercising any oversight over the first commercially-available transgenic animal."); *id*. at 480 ("[T]he FDA effectively excluded ornamental fish from *any regulatory* scrutiny by drawing its authority as narrowly as possible and only covering those NADs that may pose a threat to the human food supply."); *see also id*. at 459 (arguing that the "GloFish offers a textbook example of technological progress outpacing policy formation" and reveals a "regulatory vacuum"); *id*. at 489 (arguing that transgenic animals are always "inherently different from," and therefore cannot be "substantially equivalent" to, unmodified animals, which amounts to interpreting the substantial equivalence standard as allowing only exceedingly minor alterations).

225. The supposed shift in the burden of proof, *see id*. at 477, 487, 490, is a red-herring (so to speak). Ms. Bratspies relies entirely on a single ambiguous sentence in the FDA's informal announcement ("There

¶ 62 Third, she would have us believe that the existing public concerns about GM foods become magnified in the case of transgenic animals,[226] but her basis for this assertion demonstrates nothing other than the fact that several self-anointed public interest groups stand ready to engage in scare mongering to suit their own purposes,[227] though Jeremy Rifkin remains in a class by himself among anti-biotech activists.[228] Fourth, Ms. Bratspies complains that the FDA has violated the National Environmental Policy Act (NEPA),[229] but again this reflects a serious misunderstanding of the latest case

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is no evidence that these genetically engineered zebra danio fish pose any more threat to the environment than their unmodified counterparts which have long been widely sold in the United States."), which sounds eminently reasonable even if inartfully drafted (perhaps the agency should have started this sentence with something along the lines of "FDA has been persuaded that . . . "). More generally, the agency continues to exercise traditional adulteration and misbranding authority over animal drugs even if it has concluded that they need not satisfy NADA requirements.

226. *See* Bratspies, *supra* note 219, at 462; *see also id*. at 475 ("The FDA's decision not to regulate GloFish certainly does nothing to generate public confidence that the FDA is attuned to the concerns of environmental protection.").

227. *See id*. at 462 n.15; *see also id*. at 474 (alluding to some sort of conspiracy between the agency and industry simply because an allegedly inapplicable FDA guidance document also happened to appear on the websites of the applicant and its trade association); *cf.* Christopher S. Bond, *Politics, Misinformation, and Biotechnology*, 287 SCIENCE 1201, 1201 (2000) (complaining that "a vocal, aggressive – and in some cases, lawless – group of advocacy organizations seeks to discredit and eliminate biotechnology"); Charles A. Deacon & Emilie K. Paterson, *Emerging Trends in Biotechnology Litigation*, 20 REV. LITIG. 589, 601 (2001) (identifying these organizations); *id*. at 602 ("When barraged with sensationalistic news stories and overblown allegations by anti-biotech groups, consumers' suspicions about genetically engineered food and other aspects of biotechnology are naturally raised."); Miskiel, *supra* note 147, at 241-42 & nn.115-16 (citing among others JAMES T. BENNETT & THOMAS J. DILORENZO, THE FOOD AND DRINK POLICE – AMERICA'S NANNIES, BUSYBODIES AND PETTY TYRANTS (1999)); Charles J. Grossman, Editorial, *Genetic Engineering and the Use of Bovine Somatotropin*, 264 JAMA 1028, 1028 (1990) (calling it "wrong for special-interest groups to play on the health and safety fears of the public to further their own ends"); David Barboza, *Biotech Companies Take on Critics of Gene-Altered Food*, N.Y. TIMES, Nov. 12, 1999, at A1; David Barboza, *Monsanto Sued over Use of Biotechnology in Developing Seeds*, N.Y. TIMES, Dec. 15, 1999, at C1 ("The real force behind the [farmers'] suit is a coalition of environmental groups, including Greenpeace."); Colin Nickerson, *Potatoes, Pesticides Divide Island*, BOSTON GLOBE, Aug. 30, 2000, at A1 (reporting that farmers "feel frustrated by environmental activists who blast pesticide use but have prevented farms from switching to genetically modified potato resistant to beetles and blight"). For my decidedly jaundiced views about the motivations and tactics of these consumer activist organizations, see Lars Noah, *Rewarding Regulatory Compliance: The Pursuit of Symmetry in Products Liability*, 88 GEO. L.J. 2147, 2154-55 & nn.30-34 (2000). As suggested previously, *see supra* note 160, most consumers in this country do not know or seem to care much about the purported hazards associated with GM foods.

228. *See* Paul S. Naik, *Biotechnology Through the Eyes of an Opponent: The Resistance of Activist Jeremy Rifkin*, 5 VA. J.L. & TECH. 5 (2000); Marilyn Chase, *Jeremy Rifkin, Usually Infuriates – and Often Bests – Biotech Industry*, WALL ST. J., May 2, 1986, at 15. For a particularly spirited and well placed attack on his demagoguery, see Singer, *supra* note 19, at 326-34 (drawing parallels to the ideologically-tinged views of T.D. Lysenko who, with Stalin's blessing, contributed to the disastrous backwardness of Soviet agriculture and genetics).

229. *See* Bratspies, *supra* note 219, at 479-86; *see also id*. at 473 (bemoaning "the FDA's casual dismissal of the environmental concerns surrounding GloFish"). Apart from repeating entirely unsubstantiated claims made by some retailers that the GloFish also had enhanced cold tolerance, *see id*. at 484 & 491, Ms. Bratspies never explains why this transgenic poses any greater risks of invasiveness than its non-transgenic imported counterpart, *cf. id*. at 483-84 & n.123 (explaining that numerous non-indigenous (and non-transgenic) species of ornamental aquarium fish have established themselves in the United States). She adds that no reason exists why the GloFish would "be dumped less often than their

law interpreting that statute.[230] Indeed, she concedes – but is "troubl[ed]" by the fact – that "the FDA's regulations categorically exclude from NEPA assessment all NAD [new animal drug] applications for drugs intended for use in nonfood animals."[231] In the unlikely event that a court concluded that the agency had misinterpreted its obligations under that statute, this arguable error in no way relates peculiarly to transgenic animals – presumably, and one would think correctly, the FDA does not go to the trouble of requiring an environmental assessment for new drugs intended to treat pets of any sort.

¶ 63 Fifth, and more generally, Ms. Bratspies fears that the agency's decision not to require premarket review of the GloFish "sets a precedent."[232] Again, she is sorely mistaken, though at a number of different levels.[233] Indeed, she should applaud rather

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unmodified kin," *id*. at 484, notwithstanding her earlier mention of a selling price exceeding $18 per fish, *see id*. at 458 n.4, which makes the GloFish roughly twenty times more expensive than your basic zebra danio and presumably less likely to get flushed down the toilet when the owner tires of the hobby, *see* Dawn Fallik, *GloFish Filling Trendy Tanks*, PHILA. INQUIRER, Jan. 17, 2004, at A1.

230. She does cite a decision whose facts have the nearest similarity, *see* Bratspies, *supra* note 219, at 482 (discussing *Foundation on Economic Trends v. Heckler*, 756 F.2d 143 (D.C. Cir. 1985), and observing that the GloFish case "raises eerie parallels"), but that was only a lower court decision and two decades old to boot (like her approach to interpreting statutes and regulations, this strikes me as terribly unsophisticated). Since NEPA's heyday in the judiciary, the Supreme Court has given the statute an ever narrowing interpretation and scope. *See, e.g.*, DOT v. Public Citizen, 541 U.S. 752, 767-68, 770 (2004); *see also* Bradley C. Karkkainen, *Toward a Smarter NEPA: Monitoring and Managing Government's Environmental Performance*, 102 COLUM. L. REV. 903, 906 (2002) ("The usual complaint in the legal literature is that NEPA lacks vitality because it has been 'eviscerated' over the years by a string of narrowing Supreme Court interpretations that elevated procedure over substance."); Harvey S. Bartlett, III, Note, *Is NEPA Substantive Review Extinct, or Merely Hibernating? Resurrecting NEPA Section 102(1)*, 13 TUL. ENVTL. L.J. 411 (2000). Indeed, just two years after ordering NIH to satisfy NEPA, the same lower court rejected a similar lawsuit that Jeremy Rifkin had brought against USDA. *See* Found. on Econ. Trends v. Lyng, 817 F.2d 882, 885-86 (D.C. Cir. 1987); *see also* Found. on Econ. Trends v. Thomas, 637 F. Supp. 25, 28-29 (D.D.C. 1986) (rejecting challenge to EPA authorization); Found. on Econ. Trends v. Johnson, 661 F. Supp. 107, 108 (D.D.C. 1986) (rejecting challenge to the Coordinated Framework).

231. Bratspies, *supra* note 219, at 485; *see also id*. at 491. She notes that the rule does not apply in "exceptional circumstances" and objects to the FDA's failure to so regard the GloFish case, *see id*. at 485-86, but just a few pages later Ms. Bratspies (now arguing that the agency has applied the GRAS exception too broadly) concedes that agencies should limit their invocation of waivers, *see id*. at 489 n.147, the use of which represents a highly discretionary judgment that, in any event, courts will not blithely second guess. In the one recent NADA review that involved scrutiny of environmental and other secondary effects, the agency also failed to find exceptional circumstances that would necessitate an environmental impact statement under NEPA. *See* Stauber v. Shalala, 895 F. Supp. 1178, 1194-96 (W.D. Wis. 1995); *see also* Gilhooley, *supra* note 141, at 1120-21 (discussing the extent to which the FDA considers environmental effects).

232. *See* Bratspies, *supra* note 219, at 460; *id*. at 479 (explaining that "the FDA ripped a large hole in the regulatory net" and that "proponents of other transgenic animals have already seized on GloFish as a precedent"); *id*. at 490 (arguing that superimposing a substantial equivalence inquiry at the outset "may well eviscerate the FDA's statutory duty to regulate NADs"). Separately, her concern that the GM zebra danio may have adverse effects when sold in its native India, *see id*. at 485, seems entirely irrelevant to the choices made by domestic regulatory officials.

233. First, as she herself seems to recognize elsewhere in her article, the FDA's brief announcement hardly represents a reasoned decision entitled to much weight – instead, it amounts to little more than a poorly elaborated and essentially informal decision declining to exercise jurisdiction. *See id*. at 459; *id*. at 483 ("The FDA's three sentence opinion plainly dismissed out of hand all the complex questions surrounding this kind of intentional release."); *cf*. *id*. at 475 ("[T]he fact that the FDA could dismiss the first transgenic animal so lightly suggests that it would be a mistake to make too much of the language in

than condemn the agency for its tactical sophistication: the FDA might have realized that the GloFish would represent a weak test case (because it seemed so trivial) should its sponsor later pursue a petition for review – a court order invalidating the agency's dubious extension of jurisdiction would set a genuine precedent that could hamper its ability to tackle truly important transgenic animals in the future.[234] Sixth, she suggests that the FDA's decision violates separation of powers principles.[235] As I have argued elsewhere, precisely the opposite is the case.[236]

¶ 64 Finally, Ms. Bratspies concludes that Congress should involve the EPA and the U.S. Fish and Wildlife Service (FWS) of the Department of the Interior,[237] a curious

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this [unrelated] guidance document."). Second, the rule of *stare decisis* operates more weakly in limiting an agency's range of discretion. *See* Lars Noah, *Treat Yourself: Is Self-Medication the Prescription for What Ails American Health Care?*, 19 HARV. J.L. & TECH. 359, 384-85 (2006); *see also* Lars Noah, *Divining Regulatory Intent: The Place for a "Legislative History" of Agency Rules*, 51 HASTINGS L.J. 255, 284-99 (2000); *cf*. *supra* note 60 (citing case law demanding consistency by the FDA). Third, her reference to the FDA rule concerning the binding nature of advisory opinions, *see* Bratspies, *supra* note 219, at 476 n.78 (citing 21 C.F.R. § 10.85, and arguing that this obligates the agency to abide by the position it announced in 1986 in connection with the publication of the Coordinated Framework that it would invoke its new animal drug authority); *see also id*. at 489-90 (regarding this statement as a conclusion that transgenic animals invariably qualify as *new* animal drugs), would not apply in this context, *see* Noah, *supra* note 78, at 114, 118-20, 127-40 (describing though criticizing this change in FDA policy). Fourth, even if the agency intended to set a precedent, it appears to have narrowed its scope to only non-food transgenic animals (or just pet fish) because, as mentioned previously, the FDA has undertaken a thorough review of the NADA for GM salmon.

234. Apparently, during the first term of the current Bush administration, the FDA's chief counsel had balked at the NADA strategy because it would necessitate a "creative interpretation" of the governing statute, preferring the informal consultation approach used for biotech foods. *See* Gillis, *supra* note 31, at E3; *cf*. Bratspies, *supra* note 219, at 472 (conceding that the FDA's enabling statute "provide[s], at best, hazy authority for regulating animal biotechnology"); *id*. at 471 ("[M]any transgenic organisms confound conventional regulatory categories . . . , [so] regulators rely on increasingly creative interpretations of these existing laws.").

235. *See* Bratspies, *supra* note 219, at 491-92. Again, her rhetoric attempts to conceal the silliness of the argument (it's enough to make anyone who knows anything about administrative law cringe): "With this decision, the potential for arbitrary agency behavior has *skyrocketed*, and unfortunately so has the likelihood of irreversible environmental harm." *Id*. at 492 (emphasis added). Of course, the premise for this constitutional argument depends entirely on agreeing with her prior (and highly debatable) claims that the FDA has failed to enforce the plain terms of the FDCA and NEPA. Indeed, Ms. Bratspies never attempts to explain how to reconcile this position with her earlier concession about the weakness underlying the agency's claim to any jurisdiction in the first place. *See id*. at 471-72.

236. *See* Lars Noah, *Interpreting Agency Enabling Acts: Misplaced Metaphors in Administrative Law*, 41 WM. & MARY L. REV. 1463, 1484-530 (2000); *id*. at 1521-22 ("Such an asymmetry in [applying *Chevron* to 'jurisdictional' questions] would make sense if the Supreme Court was more concerned about the undue expansion as opposed to contraction of agency powers . . . [and] insofar as one thinks it implausible that Congress would have given agencies free reign to expand their range of operations."); *see also id*. at 1476-77, 1488 (explaining that the FDA has a long and somewhat checkered history of expansively interpreting the reach of its delegated jurisdiction). Even if not understood as an exercise of healthy institutional restraint by declining uncertain jurisdiction, courts routinely accept the inevitably of agency discretion in implementing a statute, and agencies surely can count on substantial judicial deference in the biotechnology arena. *See* William H. von Oehsen, III, *Regulating Genetic Engineering in an Era of Increased Judicial Deference: A Proper Balance of the Federal Powers*, 40 ADMIN. L. REV. 303 (1988).

237. *See* Bratspies, *supra* note 219, at 504 ("Ideally Congress would decide to channel regulatory decisions [over transgenic animals] to the EPA and Fish and Wildlife Service – agencies with some expertise in assessing environmental safety and risks."). The FWS previously concluded that it lacked the

suggestion given the frequent complaints about the jurisdictional incoherence that besets this area. Although any one of these errors may not prove fatal to her overall thesis (and quibbles about several of her subsidiary claims entirely aside), in the aggregate they suggest that she has made much ado about nothing. The FDA deserves praise for not wasting its precious time and energy on this decidedly small fry.

2. New Tools for Bioterrorists

¶ 65 In the wake of terrorist attacks in the United States, the federal government became alarmed about the potential use of biological agents such as anthrax, smallpox, and tularemia. Although the risk of bioterrorism has received substantial attention and an influx of resources designed to detect and respond to such a threat, most experts conclude that this country remains woefully unprepared.[238] Even enhanced preparation may not, however, do much to guard against an even more ominous possibility – namely, the use of pathogens genetically altered for greater virulence, an ability to escape detection, or resistance to available treatments.[239] The risks remain difficult to quantify, but the spread of expertise in genetic engineering techniques and the ready availability of the necessary raw materials makes the threat hard to dismiss as entirely speculative.[240] It also raises the possibility that demands of national security will lead to restrictions on certain types of

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authority to regulate transgenic animals. *See* Dresser, *supra* note 182, at 429 n.225. Even if Congress delegated to it some authority in the future, this agency surely would not undertake an analysis of human food safety questions, which would mean the continued involvement of the FDA or USDA.

238. *See* John Mintz & Joby Warrick, *U.S. Unprepared Despite Progress, Experts Say*, WASH. POST, Nov. 8, 2004, at A1; Bernard Wysocki, Jr., *US Struggles for Drugs To Counter Biological Threats*, WALL ST. J., July 11, 2005, at A1; *see also* Raymond J. Baxter et al., *Is the U.S. Public Health System Ready for Bioterrorism? An Assessment of the U.S. Public Health Infrastructure and its Capacity for Infectious Disease Surveillance*, 2 YALE J. HEALTH POL'Y L. & ETHICS 1, 17 (2001); Symposium, *Eliminating Legal, Regulatory, and Economic Barriers to Biodefense Vaccine Development*, 8 J. HEALTH CARE L. & POL'Y 1 (2005). As happened with the Orphan Drug Act, biotech startups have shown the most interest in federal incentives for developing drug treatments against biowarfare agents. *See* Michael Barbaro, *Bioshield Too Little for Drug Industry: Companies Want More Protection from Financial Loss*, WASH. POST, July 26, 2004, at E1; Marc Kaufman, *U.S. Awards Anthrax Vaccine Deal: Under Project Bioshield, Firm Will Make Doses for Stockpile*, WASH. POST, Nov. 5, 2004, at A4.

239. *See* Lawrence O. Gostin, *When Terrorism Threatens Health: How Far Are Limitations on Personal and Economic Liberties Justified?*, 55 FLA. L. REV. 1105, 1116 & n.42 (2003); David A. Koplow, *That Wonderful Year: Smallpox, Genetic Engineering, and Bio-terrorism*, 62 MD. L. REV. 417 (2003); Mintz & Warrick, *supra* note 238, at A1 (reporting about "the prospect of new genetically engineered pathogens that could be both more deadly and more difficult to detect and treat"); Oliver Morton, *Biology's New Forbidden Fruit*, N.Y. TIMES, Feb. 11, 2005, at A25. In yet another NEPA challenge, Jeremy Rifkin's group brought a claim against the U.S. Department of Defense over alleged rDNA biowarfare research. *See* Found. on Econ. Trends v. Weinberger, 610 F. Supp. 829 (D.D.C. 1985).

240. *See* Joby Warrick, *Custom-Built Pathogens Raise Bioterror Fears*, WASH. POST, July 31, 2006, at A1; *see also* Antonio Regalado, *Next Dream for Venter: Create Entire Set of Genes from Scratch*, WALL ST. J., June 29, 2005, at A1 (describing a new venture that hopes to commercialize such completely man-made microbes); Rick Weiss, *Researchers Create Virus in Record Time: Organism Not Dangerous to Humans*, WASH. POST, Nov. 14, 2003, at A10 (describing improved DNA-linking techniques that allowed scientists to create "a fully infectious virus from off-the-shelf ingredients in just two weeks," far more quickly than previous work that had succeeded in stitching together a polio virus from scratch, and speculating about possible future uses of synthetic microbes); *supra* note 13 (discussing synthetic biology).

biotech research.[241]

II. REACTIVE REGULATION: LEAVING TORT LAW TO MOP UP ANY MESSES

¶ 66 Inevitably, courts will play a role in defining the duties of sellers and users of biotechnologies. If direct regulation successfully manages the risks and benefits associated with biotechnology, they may play only a supporting role; otherwise, courts may have to step into the breach, so to speak, and allow private litigants to help shape public policy in the field, as some have argued happened inappropriately in response to an earlier generation's enthusiastic embrace of organic chemicals.[242] Although petrochemicals and similar compounds became mainstays of agriculture and industry in the middle of the last century, legislators and regulatory officials only responded in a belated (reactive) and incomplete fashion,[243] leaving courts to develop a variety of specialized doctrines to address the resulting "toxic tort" cases that later arose. Some of these special rules may have grown from judicial misapprehensions that this type of litigation presented unique challenges.[244] Even if genuinely new rules were needed to cope with such cases, the broader lesson has merit – leaving courts to deal with a problem after the fact may not represent a sensible response to an emerging technology.[245]

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241. *See* Henry C. Kelly, *Terrorism and the Biology Lab*, N.Y. TIMES, July 2, 2003, at A25; *see also* 42 C.F.R. pt. 73 (2005).

242. *See* Joan M. Ferretti, *Looking for the Big Picture – Developing a Jurisprudence for a Biotechnological Age*, 10 PACE ENVTL. L. REV. 711, 722 (1993) (explaining that courts are poorly equipped to tackle these questions of public policy, especially in light of endemic scientific uncertainties); *id*. at 735 (criticizing "the backwardness of our regulatory approach [to organic chemicals] and the judiciary's role in playing catch up"). Adapting tort doctrine to new types of cases or to accommodate new types of information raises the prospect of both major and minor errors in resolving disputes. *See* Lars Noah, *An Inventory of Mathematical Blunders in Applying the Loss-of-a-Chance Doctrine*, 22 REV. LITIG. 369 (2005).

243. *See* Ferretti, *supra* note 242, at 721 ("The legislative and subsequent regulatory responses to organic chemical technology did not take place until the mid-1970s, thirty years after the first wide-scale uses of organic chemicals."); *id*. at 740 ("In the case of organic chemical technology, the respective regulatory packages were too late. As a result, they were costly, cumbersome, backward-looking, and incomplete."); *see also id*. at 713-16 (explaining why organic chemical regulation offers relevant lessons for biotechnology); *id*. at 715 ("[B]iotechnology will also be complicated by the difficulties of identification, detection, and latency of manifestation, which complicate evaluations in organic chemical technology.").

244. *See id*. at 735-38 (questioning the need for modified evidentiary rules governing the admissibility of expert testimony and government records in toxic tort cases).

245. *See id*. at 744-45 ("In light of our organic chemical experience, a new strategy is necessary to replace this current patchwork approach. . . . Trying to utilize old statutes to develop a forward-looking regulatory approach would present serious risks.").

With biotechnology, the opportunity is ripe for the development of a lean, efficient, and finely tuned regulatory approach, one which is flexible enough to accommodate diverse processes and fluid enough to deal with inherent scientific complexity. The industry is young enough to grow with regulation and to anticipate regulatory costs in investment and insurance decisions.

Id. at 740; *see also* Mostow, *supra* note 14, at 265-66 ("In the long run, waiting for a crisis might be worse for the developing [biotechnology] industry than taking some time now to formulate a more rational regime.").

¶ 67 As with direct regulation, courts resolving tort litigation may have to decide whether any injuries caused by the products and processes of biotechnology require fundamental changes in existing doctrine.[246] Some commentators contend that the advent of GMOs necessitates basic alterations in current tort law. For instance, Katharine van Tassel recently argued that the rules of products liability applicable to foods must adjust to ensure that labeling appear on all bioengineered foods.[247] She starts from the premise that significant risks accompany the consumption of these products, asserting with no apparent foundation that "large numbers of consumers may have been, and may continue to be, the victims of serious injuries from the ingestion of biotech food."[248] Her article focuses on allergic reactions and offers this startling claim: "The incidence of food allergies reported to researchers has risen significantly over the past ten years. This increase parallels the proliferation of biotech foods on U.S. grocery shelves."[249] This suggested association is reminiscent of the widely publicized and entirely discredited claims made by a persistent critic of the non-nutritive sweetener aspartame that an increase in reports of brain cancer had coincided with the increase in domestic

246. *See* Julie A. Davies & Lawrence C. Levine, *Biotechnology's Challenge to the Law of Torts*, 32 MCGEORGE L. REV. 221, 221-22 (2000); *id*. at 222 ("We join those commentators who have determined that there is nothing so special about biotechnology and the products it creates that special treatment is merited.").

247. *See* Katharine van Tassel, *The Introduction of Biotech Foods to the Tort System: Creating a New Duty To Identify*, 72 U. CIN. L. REV. 1645 (2004).

248. *Id*. at 1688; *see also id*. at 1696-97 (offering only a brief reference to concerns about antibiotic resistance as another potential human health risk before elaborating on ecological impacts); *id*. at 1667, 1687 (suggesting in all apparent seriousness that American consumers serve as unwitting guinea pigs in a nationwide feeding experiment); *cf*. Lars Noah, *Informed Consent and the Elusive Dichotomy Between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361, 362-63, 377-408 (2002) (arguing that experimentation pervades medical practice).

249. van Tassel, *supra* note 247, at 1662 (footnotes omitted). To her credit (and at my urging as an unacknowledged reviewer of an earlier draft of her manuscript), Ms. van Tassel conceded in an accompanying footnote that "this parallel could be purely coincidental and this increase could be due to any number of other environmental factors. The point is that the means to create a scientific study to eliminate this possibility does not exist by virtue of the current regulatory scheme." *Id*. at 1662 n.98. What she fails to recognize, however, is that researchers have proposed a number of testable alternative hypotheses to account for the increased frequency of reported allergies, ranging from expanded diagnostic categories to larger numbers of children with underdeveloped immune systems. (Moreover, the absence of disclosures in GM food labeling hardly prevents research into the question, as revealed by the StarLink litigation – she makes only a passing reference to that episode, *see id*. at 1660 & n.94, but curiously never mentions the resulting litigation.) Finally, Ms. van Tassel emphasizes that most processed foods contain GM ingredients, but, in the next breath, she argues that the absence of generic disclosure labeling makes it difficult to determine whether an association exists with reported allergic reactions. *See id*. at 1662-63; *see also* Kirsten S. Beaudoin, Comment, *On Tonight's Menu: Toasted Cornbread with Firefly Genes? Adapting Food Labeling Law to Consumer Protection Needs in the Biotech Century*, 83 MARQ. L. REV. 237, 276 (1999) ("Ideally, [federally mandated] labels should facilitate epidemiological studies to detect any increase in allergies or diseases linked to GM foods."). If, as she hopes, sellers respond to the threat of tort liability by affixing generic GM disclosure labels to most or all food products, it will do absolutely nothing to promote research into the suspected allergenicity of GM foods. Indeed, as experience with other food-use substances suggests, an effort to promote adverse event reporting will generate numerous unverifiable or entirely spurious consumer complaints. *See* Linda Tollefson, *Monitoring Adverse Reactions to Food Additives in the U.S. Food and Drug Administration*, 8 REG. TOXICOLOGY & PHARMACOLOGY 438, 441-44 (1988) (noting that the majority of initial reports concerned aspartame and sulfiting agents).

consumption of this food additive.[250] Even if we assume, just for the sake of argument, that some association existed, the emerging "epidemic" of food allergies allegedly caused by GMOs pales in comparison to risks that arise from, for instance, food-borne microbial hazards.[251]

¶ 68 Apart from its overly alarmist account of the hazards posed by GM foods, Ms. van Tassel's article suffers from a variety of serious substantive flaws. For instance, she argues that courts should switch to a risk-utility test for judging design defects in bioengineered foods in lieu of the consumer expectations test that still prevails in food cases.[252] Although it may well make sense to alter the design defect rules for all processed foods, Ms. van Tassel never persuasively justifies carving out GMOs for

250. *See* Robert Frank, *Aspartame Critic Urges More Study of the Sweetener*, WALL ST. J., Nov. 8, 1996, at B5E; Melanie Warner, *Study Finds No Cancer Link to Sweetener*, N.Y. TIMES, Apr. 8, 2006, at C4; *see also* Ballinger v. Atkins, 947 F. Supp. 925, 929 (E.D. Va. 1996) (excluding expert testimony linking plaintiff's alleged neurological injury to consumption of aspartame). As it happens, aspartame is a biotech-derived food additive. *See* Nell Henderson, *Aspartame: A Sweet for Two Biotech Firms*, WASH. POST, Nov. 5, 1984, § 5, at 1. Perhaps that explains the observed increase in brain tumors! ;->

251. *Compare* van Tassel, *supra* note 247, at 1658 ("As many as two hundred people in the United States die each year from allergic reactions to food . . . ."); *with* Pathogen Reduction: Hazard Analysis and Critical Control Point (HACCP) Systems, 60 Fed. Reg. 6774, 6781 (1995) (reporting CDC estimates that five million Americans become ill each year from food-borne pathogens just in meat and poultry, which results in 4,000 deaths); Merrill & Francer, *supra* note 51, at 68 (citing 1999 CDC estimates that 325,000 Americans are hospitalized and 5,000 die annually from food-borne illnesses); Jane Zhang, *When Eating Your Vegetables Makes You Sick*, WALL ST. J., Nov. 30, 2005, at D1; *see also* Peter Passell, *The American Sense of Peril: A Stifling Cost of Modern Life*, N.Y. TIMES, May 8, 1989, at A1 (contrasting the undue preoccupation with low risks from pesticide residues with the greater hazards from natural contaminants in food).

252. Courts gradually have moved away from the old foreign/natural distinction in these cases but continue to abide by the consumer expectations test. *See, e.g.*, Clime v. Dewey Beach Enters., Inc., 831 F. Supp. 341, 347-50 (D. Del. 1993); Mexicali Rose v. Superior Court, 822 P.2d 1292 (Cal. 1992); Simeon v. Doe, 618 So. 2d 848, 851 (La. 1993); Phillips v. W. Springfield, 540 N.E.2d 1331 (Mass. 1989); *see also* Jane Massey Draper, *Liability for Injury or Death Allegedly Caused by Food Product Containing Object Related to, but Not Intended To Be Present in, Product*, 2 A.L.R.5th 189 (1992 & Supp. 2005); Jane Massey Draper, *Liability for Injury or Death Allegedly Caused by Spoilage, Contamination, or Other Deleterious Condition of Food or Food Product*, 2 A.L.R.5th 1 (1992 & Supp. 2005). One can, however, read the new *Restatement* as applying the consumer expectations test only to alleged manufacturing defects in food, while using the same risk-utility test for design defects that it applies to other products. *See* RESTATEMENT (THIRD) OF THE LAW OF TORTS: PRODUCTS LIABILITY § 7 & cmt. a (1998) [hereinafter PRODUCTS RESTATEMENT]. Without expending undue effort to parse the intent behind this language, elsewhere the reporters recognized that inadvertent design flaws shared by all units (such as a product's blatant failure "to perform its manifestly intended function") have more in common with single-unit manufacturing defects than with alleged shortcomings in conscious product design choices. *See id.* § 2 cmt. b, § 3 illus. 3. Furthermore, putting aside the complexities posed by variable dishes served in restaurants, the case law involving processed and packaged foods does not narrowly confine the consumer expectations test only to manufacturing defect claims, though (recent fast-food litigation aside) one rarely encounters situations where the plaintiff alleges that an unadulterated product presented an excessive preventable danger. *Cf.* RESTATEMENT (SECOND) OF THE LAW OF TORTS § 402A cmt. i (1965) (justifying the blackletter modification of the phrase "defective condition" with "unreasonably dangerous" as a means for distinguishing the risks posed by contaminants in foodstuffs from their obvious chronic health effects); Richard C. Ausness, *Tell Me What You Eat, and I Will Tell You Whom To Sue: Big Problems Ahead for "Big Food"?*, 39 GA. L. REV. 839, 851-58 (2005).

separate treatment.[253] In addition, because comprehensive disclosure represents her goal, the last thing you would want to do is shift away from the old consumer expectations standard.[254] Indeed, as suggested by her own description of risk-utility balancing applied to GM foods,[255] the failure to employ available processes of biotechnology could render conventional (non-biotech) foods containing naturally occurring toxins, allergens, or injurious pesticide residues subject to claims for defective design.[256] Thus, a shift to a risk-utility standard and its search for a reasonable alternative design could result in greater reliance on GMOs in processed foods, unless the biotech versions brought with them actual, as opposed to entirely speculative, offsetting disutilities.[257]

¶ 69 Finally, Ms. van Tassel's discussion of the decisional law involving the limited duties to design around or warn of allergens, which she repeatedly characterizes as an "immunity,"[258] bears little resemblance to what the courts do in such products liability

253. *See* van Tassel, *supra* note 247, at 1678-79. Indeed, at one point she seems to recognize as much. *See id*. at 1676 ("With the advent of the food processing industry as we know it today, a large portion of the American public's dietary intake consists of highly processed, pre-packaged, and pre-prepared food."). What appears to lead her astray in the analysis is a tendency to regard traditional food products as little more than raw produce (or, conversely, variable dishes prepared in restaurants, which raises related questions about the sales/service distinction), *see id*. at 1673, and compare these to the more consciously designed and arguably less variable GM versions of the same agricultural commodities (e.g., fresh tomatoes). The use of natural components or raw materials hardly distinguishes food from any number of other consumer goods. *See* PRODUCTS RESTATEMENT, *supra* note 252, § 19 cmt. b (providing that raw materials – including but not limited to farm produce – and diseased animals that cause personal injury constitute "products" for liability purposes). If, instead, we focus on highly processed foods mass produced and packaged on assembly lines by large companies for distribution through grocery stores (e.g., breakfast cereals or frozen dinners), whether or not they include GMOs among their ingredients, then it makes little sense to single out GM foods for distinctive treatment in tort law.

254. If ordinary purchasers currently do not know about the prevalence of GM foods and ingredients (or their purported risks), then the consumer expectations test would ease plaintiffs' burden in pursuing a design defect claim against unlabeled food products and prevent the seller from introducing evidence of the societal benefits attained through genetic engineering of raw agricultural commodities. More broadly, suggestions made by other commentators in favor of switching from a "product" to a "process" orientation in regulating biotechnology would backfire in the domain of tort law insofar as this could weaken strict products liability's focus on the finished good and instead resurrect a negligence-based inquiry into the reasonableness of only the manufacturer's conduct in the production process.

255. *See* van Tassel, *supra* note 247, at 1694-96.

256. *See, e.g.*, Jikun Huang et al., *Insect-Resistant GM Rice in Farmers' Fields: Assessing Productivity and Health Effects in China*, 308 SCIENCE 688 (2005); Andrew Pollack, *Gene Jugglers Take to Fields for Food Allergy Vanishing Act*, N.Y. TIMES, Oct. 15, 2002, at F2.

257. *See* Drew L. Kershen, *The Risks of Going Non-GMO*, 53 OKLA. L. REV. 631, 635-36, 646 (2000). For instance, because insect damage to ears of corn allows growth of a mycotoxin that produces fumonisin, corn modified for enhanced pest-resistance has significantly lower concentrations of this suspected carcinogen. *See* Drew L. Kershen, *Health and Food Safety: The Benefits of Bt-Corn*, 61 FOOD & DRUG L.J. 197 (2006).

258. *See* van Tassel, *supra* note 247, at 1679-86, 1690 (also repeatedly blaming the FDA for failing to require the labeling of all GM foods); *id*. at 1685 ("No labeling means that the biotech industry can remain blissfully unaware of any risks associated with its products. And as long as there is no knowledge of risks, biotech products will not be labeled."); *id*. at 1686 ("Unfortunately, the reasonable consumer expectation test carries with it the idiosyncratic allergic response doctrine. This doctrine, coupled with the FDA's failure to require labeling for biotech food, creates an unintentional immunity from liability for harm from biotech food."); *id*. at 1688 ("The tort system as currently constituted will not compensate any of these victims for their injuries until a critical mass of injured individuals is achieved."). It would be equally

cases,[259] and it provides no foundation for her effort to secure disclosure labeling for all GM foods. The rule requiring a "substantial" or "appreciable" number of affected consumers simply amounts to something akin to a *de minimis* threshold, and it operates more strongly to protect sellers against demands for redesigns than for warnings.[260] Moreover, she mistakenly assumes that epidemiological studies offer the only method for discerning cause-and-effect (or that such studies could proceed only if consumers had access to disclosures in labeling); instead, of course, a seller can know or should know of a risk based on information gleaned from sources other than retrospective human population studies.[261] Her discussion also fails to appreciate that sellers of other products subsequently linked to diseases at first may escape liability by virtue of "knowability" (state-of-the-art) as a prerequisite for the imposition of liability, sometimes also in areas where regulatory agencies have failed to impose any disclosure requirements, so to point out that sellers initially may get away with causing one or more injuries hardly distinguishes biotech foods.[262]

(in)accurate to characterize unknowable risks, impossible redesigns, lack of causation, or other gaps in a plaintiff's prima facie case as "immunities."

259. *See, e.g.*, Goodman v. Walco Tool & Eng'g Co., 614 N.E.2d 42, 48-49 (Ill. App. Ct. 1993) (noting that courts recently had relaxed this duty limitation); Jones v. Gen. Motors Corp., 939 P.2d 608, 618 (Or. 1997) (denying the defendant's motion for summary judgment, which had invoked the idiosyncratic reaction defense); *see also* PRODUCTS RESTATEMENT, *supra* note 252, § 2 cmt. k ("The degree of substantiality is not precisely quantifiable. Clearly the plaintiff in most cases must show that the allergic predisposition is not unique to the plaintiff. . . . The more severe the harm, the more justified is a conclusion that the number of persons at risk need not be large to be considered 'substantial' so as to require a warning."); Allan E. Korpela, Annotation, *Products Liability: Strict Liability in Tort Where Injury Results from Allergenic (Side-Effect) Reaction to Product*, 53 A.L.R.3d 298 (1973 & Supp. 2005). To further confuse the issue, Ms. van Tassel repeatedly and incorrectly lumps toxins together with allergens.

260. *See* James A. Henderson, Jr., *Process Norms in Products Liability Litigation: Liability for Allergic Reactions*, 51 U. PITT. L. REV. 761, 777-82 (1990); Michael K. Barrett, Comment, *Latex Gloves: Medical-Legal Issues for Health Care Professionals*, 22 J. LEGAL MED. 263, 269-73 (2001); Jonathan Bridges, Note, *Suing for Peanuts*, 75 NOTRE DAME L. REV. 1269, 1277-81 (2000).

261. For instance, a seller may be charged with knowledge based on information concerning risks associated with a chemically similar product. *See, e.g.*, Wagner v. Roche Labs., 671 N.E.2d 252, 256-58 (Ohio 1996) (Accutane); Barson v. E.R. Squibb & Sons, 682 P.2d 832, 836 (Utah 1984) (reports that progesterone caused birth defects should have alerted manufacturer of progesterone-derivative to its teratogenic potential); *see also* Mulligan v. Lederle Labs., 786 F.2d 859, 864-65 (8th Cir. 1986) (sustaining verdict for plaintiff where the manufacturer previously had received reports of similar but not identical adverse reactions). More generally, a number of courts have imposed a related duty to conduct safety tests. *See, e.g.*, Lindsay v. Ortho Pharm. Corp., 637 F.2d 87, 91 (2d Cir. 1980) ("The duty is a continuous one, requiring the manufacturer to keep abreast of the current state of knowledge of its products as gained through research, adverse reaction reports, scientific literature, and other available methods."); Kociemba v. G.D. Searle & Co., 707 F. Supp. 1517, 1528-29 (D. Minn. 1989) ("[T]he duty to test is a subpart . . . of the duty to warn."); *In re* Tetracycline Cases, 747 F. Supp. 543, 550 (W.D. Mo. 1989); Medics Pharm. Corp. v. Newman, 378 S.E.2d 487, 488-89 (Ga. Ct. App. 1989); *see also* PRODUCTS RESTATEMENT, *supra* note 252, § 2 cmt. m ("The harms that result from unforeseeable risks . . . are not a basis of liability. Of course, a seller bears responsibility to perform reasonable testing prior to marketing a product and to discover risks and risk-avoidance measures that such testing would reveal. A seller is charged with knowledge of what reasonable testing would reveal.").

262. *See, e.g.*, Burlison v. Warner-Lambert Co., 842 F.2d 991 (8th Cir. 1988) (cough drop manufacturer had no duty to warn in the absence of evidence that it knew or should have known of possible allergic reactions); Griggs v. Combe, Inc., 456 So. 2d 790, 792 (Ala. 1984) (OTC drug manufacturer "had no duty to warn of a possible allergic reaction which it had no reason to suspect might occur"); Moore v. Vanderloo, 386 N.W.2d 108, 116 (Iowa 1986); Castrignano v. E.R. Squibb & Sons, Inc., 546 A.2d 775,

¶ 70 Ms. van Tassel mistakenly believes that a shift from a consumer expectations test to risk-utility design defect scrutiny will eliminate this purported immunity.[263] As she recognizes, however, those jurisdictions that have adopted the latter test still would regard a small aggregate risk of allergenicity as inconsequential relative to the disutilities involved in any redesign, and unknowable risks of allergenicity would trigger no duties whatsoever. Nonetheless, Ms. van Tassel remarkably proposes that the identical product with an added disclosure in labeling would amount to a reasonable alternative design (RAD).[264] Instead, this supposed alternative design relates to the entirely separate inquiry about so-called informational defects, which include but are not limited to a duty to warn of risks.[265] Even if such a relabeled product qualified as a RAD, the plaintiff also would have to demonstrate that the redesign likely would have reduced the risk of injury, an issue that she never bothers to address.[266]

¶ 71 Ultimately, Ms. van Tassel urges using tort litigation, though apparently unhinged from the requirement of showing injury to a particular victim, as a roundabout means of forcing companies to reveal information that the FDA has decided does not qualify as material.[267] If a seller breaches this new "duty to identify" the presence of a GM

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782 (R.I. 1988) (refusing to hold the manufacturer of DES liable "for failure to warn of risks inherent in a drug [because] it neither knew nor could have known by the application of scientific knowledge available at the time of distribution that the drug could produce the undesirable effects suffered by plaintiff"); *see also* Grenier v. Med. Eng'g Corp., 243 F.3d 200, 205 (5th Cir. 2001) (dismissing the plaintiff's failure-to-warn claim because she "presented no evidence about the cause, frequency, severity, or consequences of 'gel bleed' with regard to the implants at issue in this case"); Donald G. Gifford, *The Peculiar Challenges Posed by Latent Diseases Resulting from Mass Products*, 64 MD. L. REV. 613 (2005).

263. *See* van Tassel, *supra* note 247, at 1693 ("The first and most satisfying result of applying risk/utility balancing to evaluate harm from the ingestion of biotech food is that the preclusive effect of the idiosyncratic reaction defense is bypassed.").

264. *See id*. at 1691, 1693 & n.215; *see also id*. at 1698-99 (conceding that the accompanying need to segregate and trace GM foods would impose some additional expense).

265. *See* PRODUCTS RESTATEMENT, *supra* note 252, § 2 cmt. k ("Cases of adverse allergic or idiosyncratic reactions involve a special subset of products that may be defective because of inadequate *warnings*. . . . When the presence of the allergenic ingredient would not be anticipated by a reasonable user or consumer, warnings concerning its presence are required." (emphasis added)); *cf*. Lars Noah, *Authors, Publishers, and Products Liability: Remedies for Defective Information in Books*, 77 OR. L. REV. 1195, 1205-08, 1211-15 (1998) (describing and criticizing the well-entrenched judicial tendency to differentiate between the tangible and intangible aspects of consumer products).

266. *Cf*. Lars Noah, *The Imperative To Warn: Disentangling the "Right To Know" from the "Need To Know" About Consumer Product Hazards*, 11 YALE J. ON REG. 293, 361-74, 391-400 (1994) (delineating shortcomings with labeling as a method of communicating information to purchasers); *id*. at 297 ("If a risk is in fact trivial, no information need be provided. . . . At present, however, warning statements often are mandated in situations where either more or less stringent regulatory alternatives would seem more appropriate."). Let us not forget that these issues already get plenty of attention in the media, but, if the average American does not pay attention to such matters when reported in the newspaper, then it seems entirely implausible to suggest that increasingly crowded labels on food will make any bit of difference. *Cf*. Emily Robertson, Note, *Finding a Compromise in the Debate over Genetically Modified Food: An Introduction to a Model State Right-To-Know Act*, 9 B.U. J. SCI. & TECH. L. 156, 177 (2003) (recommending, instead of labeling that might stigmatize GM foods unfairly, the creation of a database accessible to interested consumers that provides disclosures concerning the presence of GMOs in listed food products).

267. *See* van Tassel, *supra* note 247, at 1647-48, 1700, 1704-05 (advocating a new common law "duty to identify"); *id*. at 1690 ("As a legislative or regulatory solution appears unlikely, the key to cutting

ingredient in food, and one accepts her argument that the lack of labeling makes it practically impossible to link an allergic reaction to a GM food, then there still appears to be no basis for imposing liability. If, however, a seller has satisfied this new duty, and assuming for the sake of argument that this somehow later facilitates efforts to link an allergic reaction to a GM food, then again there appears to be no basis for imposing liability (assuming that the seller had no way of knowing of this possibility, though subsequent victims then might have more luck in asserting traditional failure to warn claims).

¶ 72 Other commentators instead fear that existing tort doctrine will unduly hinder the commercialization of biotechnological innovations.[268] Biotech drugs should, however, face the same tort doctrines that apply to conventional pharmaceuticals, including those rules that insulate prescription drug products from the full brunt of strict liability.[269] In addition, some therapeutic applications of biotechnology would face only a negligence standard insofar as they involved the rendition of a service rather than the sale of a product.[270] Nonetheless, injuries caused by product flaws would trigger strict liability

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this [G]ordian knot lies with the judiciary."); *cf.* Moin A. Yahya, *Can I Sue Without Being Injured?: Why the Benefit of the Bargain Theory for Product Liability Is Bad Law and Bad Economics*, 3 GEO. J.L. & PUB. POL'Y 83, 109-13 (2005). Consumers also may not know that their foods contain pesticide or antibiotic residues or microbial contaminants or that their foods were harvested by undocumented workers or imported from another country. *Cf.* Animal Legal Defense Fund v. Provimi Veal Corp., 626 F. Supp. 278, 285-86 (D. Mass. 1986) (rejecting effort to require disclosure of livestock rearing practices). Indeed, if the goal of disclosure does not relate to genuine safety concerns but simply the remote possibility of an unforeseen allergic response or collateral issues such as environmental impacts, why stop at foods – perhaps clothing (or furniture) derived from GM cotton (or timber) needs special labeling as well (after all, if you get a rash, then you want to know who to blame). *Cf.* James Gorman, *Frankencotton, the Shirt: Coming Soon to a Wardrobe Near You*, N.Y. TIMES, May 16, 2006, at F2. Moreover, Ms. van Tassel's analysis makes the perhaps heroic assumption that the threat of tort liability meaningfully influences corporate behavior. *Cf.* Harlow, *supra* note 222, at 559 & n.33 (suggesting that biotech firms may be particularly inattentive to the deterrent effects of potential civil litigation); Zepfel, *supra* note 25, at 650 (same). *See generally* Noah, *supra* note 50, at 634 n.129 (citing conflicting views on this broader question).

268. *See* Dan L. Burk & Barbara A. Boczar, *Biotechnology and Tort Liability: A Strategic Industry at Risk*, 55 U. PITT. L. REV. 791, 794-95, 828-48 (1994); *id.* at 828 ("Biotechnology-based tort disputes, in addition to being the kind of science-laden dispute that tends to bring out the worst in the American legal system, will also be accompanied by anomalies of public perception and risk perception that are likely to distort further the adjudication process."); *id.* at 848-64 (recommending the adoption of a non-tort mechanism modeled on the National Childhood Vaccine Injury Act); James T. O'Reilly, *Biotechnology Meets Products Liability: Problems Beyond the State of the Art*, 24 HOUS. L. REV. 451, 452-53, 461-63, 465-69, 488-89 (1987); Michael D. Stovsky, Comment, *Product Liability Barriers to the Commercialization of Biotechnology: Improving the Competitiveness of the U.S. Biotechnology Industry*, 6 HIGH TECH. L.J. 363 (1991).

269. *See* Davies & Levine, *supra* note 246, at 228; Michael Traynor & Brian C. Cunningham, *Emerging Product Liability Issues in Biotechnology*, 3 HIGH TECH. L.J. 149, 177-78, 192 (1988); *see also* Noah, *supra* note 227, at 2157, 2162-63; Lars Noah, *Advertising Prescription Drugs to Consumers: Assessing the Regulatory and Liability Issues*, 32 GA. L. REV. 141, 155-61 (1997) (summarizing limitations on the duty to warn). Other applications of biotechnology also may benefit from such rules. *Cf.* Ruiz-Guzman v. Amvac Chem. Corp., 7 P.3d 795, 803-04 (Wash. 2000) (extending comment k immunity from strict products liability to certain restricted pesticides).

270. *See* Noah, *supra* note 50, at 646; *see also* Edward A. Marshall, Note, *Medical Malpractice in the New Eugenics: Relying on Innovative Tort Doctrine To Provide Relief When Gene Therapy Fails*, 35 GA. L. REV. 1277, 1299-327 (2001).

claims for manufacturing defects,[271] and tort issues peculiar to biotech products may arise from adverse environmental consequences after intentional release.[272]

III. LESSONS FOR THE NEXT WAVE: NANOTECHNOLOGY

¶ 73 Not unlike the emergence of biotechnology three decades ago, many observers have begun to hail nanotechnology as the next big thing.[273] This fairly new field involves feats of engineering at the extremely small scales occupied by atoms and simple molecules – a nanometer represents one-billionth of a meter. Nanotechnology essentially allows scientists to engineer novel molecules, and it offers more than sheer miniaturization: at these scales, quantum forces come into operation and chemical reactivity increases.[274] Using advanced electron microscopes and other tools of molecular engineering, scientists have, for instance, formed carbon atoms into unusually strong and conductive hollow tubular or spherical structures – nanotubes and fullerenes (named after Buckminster Fuller for their resemblance to his geodesic domes and nicknamed "buckyballs"). Engineers then can assemble these and other nanomaterials into various nanoscale devices.

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271. *See* Kramer v. Showa Denko K.K., 929 F. Supp. 733 (S.D.N.Y. 1996); DiRosa v. Showa Denko K.K., 52 Cal. Rptr. 2d 128 (Ct. App. 1996) (affirming a judgment for a plaintiff injured by contamination of the amino acid dietary supplement L-tryptophan after the manufacturer switched to a production process using bioengineered bacteria); *see also* Philip Raphals, *Does Medical Mystery Threaten Biotech?*, 250 SCIENCE 619 (1990).

272. *See, e.g.*, Note, *Designer Genes That Don't Fit: A Tort Regime for Commercial Releases of Genetic Engineering Products*, 100 HARV. L. REV. 1086, 1096-105 (1987) (recommending efforts to ease plaintiffs' burdens in proving causation by adopting rebuttable presumptions, requirements that firms releasing GMOs into the environment carry insurance, and applying strict liability in tandem with rules of joint and several liability); *see also* Thomas P. Redick, *Biopharming, Biosafety and Billion Dollar Debacles: Preventing Liability for Biotech Crops*, 8 DRAKE J. AGRIC. L. 115, 123-25 (2003) (focusing on the risks with pharming); *supra* notes 136-40 and accompanying text (discussing litigation triggered by the StarLink contamination episode); *cf.* Krug v. Koriel, 935 P.2d 1063 (Kan. Ct. App. 1997) (declining to impose liability on farmer who failed to limit spread of virus in wheat crop). The Vermont Senate recently passed a bill that would impose strict liability in such cases. *See* Stephen Clapp, *Washington Interest Groups Battle over Biotech in State Legislatures*, FOOD CHEM. NEWS, Apr. 18, 2005, at 1; *cf.* Jane M. Friedman, *Health Hazards Associated with Recombinant DNA Technology: Should Congress Impose Liability Without Fault?*, 51 S. CAL. L. REV. 1355, 1378-79 (1978) (favoring enactment of a federal statute imposing strict liability, though coupled with indemnification by the government); Brady L. Montalbano, Comment, *It's Not Easy Being Green – Holding Manufacturers of Genetically Modified Bentgrass Liable Under Strict Products Liability*, 14 PENN. ST. ENVTL. L. REV. 111 (2005).

273. *See* Adam Aston, *Beaming in on Nano Gold*, BUS. WK., June 27, 2005, at 122 ("Devotees call it the biggest thing since the Industrial Revolution."); *see also* Mark A. Lemley, *Patenting Nanotechnology*, 58 STAN. L. REV. 601 (2005); Michael A. van Lente, Note, *Building the New World of Nanotechnology*, 38 CASE W. RES. J. INT'L L. 173 (2006). The National Science Foundation has estimated that the annual market for products and services derived from nanotechnology will reach $1 trillion by 2015. *See* Christine Hines, *Law Firms Seek Nanotech Business*, NAT'L L.J., Nov. 17, 2003, at 11. Research grants from the U.S. National Nanotechnology Initiative have now eclipsed $1 billion annually. *See* Rick Weiss, *Nanotech Is Booming Biggest in U.S., Report Says*, WASH. POST, Mar. 28, 2005, at A6; *see also* 21st Century Nanotechnology Research and Development Act, Pub. L. No. 108-153, 117 Stat. 1923 (2003) (to be codified at 15 U.S.C. §§ 7501-7509); National Nanotechnology Initiative, *available at* http://nano.gov (last visited July 14, 2006).

274. *See* Rick Weiss, *Applications Abound for Unique Physical, Chemical Properties*, WASH. POST, Feb. 1, 2004, at A17.

¶ 74 Many of nanotechnology's most promising applications may appear in medicine.[275] As a result, the FDA again will have to play a significant role in supervising this emerging field. In fact, one of the first practical uses of nanotechnology, in sunscreens and cosmetics, unmistakably falls under this agency's jurisdiction.[276] In the future, however, nanomedicine will present the FDA with far more difficult scientific, legal, and policy challenges. Possible innovations that may defy traditional regulatory classifications include nanofoam that could enhance diagnostic imaging,[277] more precise drug delivery vehicles, and hemoglobin-carrying nanotubes as a blood substitute. If biotechnology rendered untenable the traditional distinction between drugs and biologics, then nanomedicine may do the same to the line separating devices and biologics.[278]

¶ 75 Nanotechnology can expect to share some of biotechnology's successes and growing pains, including uncertainty about consumer acceptance and possible adverse impacts.[279] For instance, it appears that some nanomaterials may persist in the environment and prove toxic to wildlife.[280] In addition, because of their extreme chemical reactivity and ability to enter cells (and pass the blood-brain barrier), legitimate concerns about adverse health consequences have arisen – like asbestos fibers, for example, nanomaterials may become dangerous when inhaled. Finally, nanotechnology

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275. *See* Barnaby J. Feder, *Doctors Use Nanotechnology To Improve Health Care*, N.Y. TIMES, Nov. 1, 2004, at C4; Stephen Heuser, *In Medicine, Small Is About To Become Big*, BOSTON GLOBE, May 8, 2006, at E1; Rick Weiss, *Nanomedicine's Promise Is Anything but Tiny*, WASH. POST, Jan. 31, 2005, at A8 ("More than 60 drugs and drug delivery systems based on nanotechnology, and more than 90 medical devices or diagnostic tests, are already being tested . . . .").

276. These products may contain tiny particles of titanium oxide, zinc oxide, and iron oxide, and British scientists have cautioned against their continued use pending further research on possible health effects, but the FDA has adopted a passive stance on the issue. *See* Sunscreen Drug Products for Over-the-Counter Human Use: Final Monograph, 64 Fed. Reg. 27,666, 27,671 (1999) ("The agency does not consider micronized titanium dioxide to be a new ingredient but considers it a specific grade of the titanium dioxide originally reviewed" in 1978 by an advisory panel.); Keay Davidson, *FDA Urged To Limit Nanoparticle Use in Cosmetics and Sunscreens*, S.F. CHRON., May 17, 2006, at A4; Rick Weiss, *Nanotechnology Precaution Is Urged: Minuscule Particles in Cosmetics May Pose Health Risk, British Scientists Say*, WASH. POST, July 30, 2004, at A2. Some commentators ridicule the inclusion of such very fine particles under the rubric of nanotechnology because they do not result from precise molecular engineering. *See* Drexler & Wejnert, *supra* note 12, at 19-20 (making the same complaint about material coatings).

277. *See* Kenneth Chang, *A Flaky New Carbon: It's Feather Light and Magnetic*, N.Y. TIMES, Apr. 6, 2004, at F3.

278. *See* John Miller, Note, *Beyond Biotechnology: FDA Regulation of Nanomedicine*, 4 COLUM. SCI. & TECH. L. REV. (2002), at 26 ("The current distinctions between 'chemical,' 'mechanical,' and 'biological' activity will be rendered useless."), *available at* http://www.stlr.org/cite.cgi?-volume=4&article=5 (last visited July 14, 2006). To be sure, the FDA already has attempted to regulate biological devices (e.g., heart valve allografts). *See* Nw. Tissue Ctr. v. Shalala, 1 F.3d 522, 536 (7th Cir. 1993); Alabama Tissue Ctr. v. Sullivan, 975 F.2d 373 (7th Cir. 1992).

279. *See* Barnaby J. Feder, *From Nanotechnology's Sidelines, One More Warning*, N.Y. TIMES, Feb. 3, 2003, at C1; David Rotman, *Measuring the Risks of Nanotechnology*, TECH. REV., Apr. 2003, at 71; Weiss, *supra* note 18, at A1; Rick Weiss, *Nanotech Group's Invitations Declined: Critics Say Effort Glosses over Risks*, WASH. POST, Oct. 28, 2004, at A4 ("Nanoscientists and activists alike have said they want to avoid a replay of the debacle over genetically engineered food, widely viewed as a classic case of an emerging science that squandered an opportunity to gain public trust.").

280. *See* Rick Weiss, *Nanoparticles Toxic in Aquatic Habitat, Study Finds*, WASH. POST, Mar. 29, 2004, at A2 (describing a study of large mouth bass in water containing fullerenes at a concentration of 0.5 parts per million that found severe brain damage caused by lipid peroxidation).

may provide another potent weapon in the arsenal of bioterrorists. Given the fact that legal institutions once again may have to play catch up,[281] some commentators have looked for lessons about appropriate regulatory strategies from the experience with biotechnology.[282] Tort liability no doubt also will come into play as an after-the-fact regulatory mechanism.

IV. CONCLUSION

¶ 76 Even when more narrowly defined to encompass only processes and products using genetic alterations, biotechnology has come to include a vast and varied landscape, one that continues to evolve. Technological revolutions do not come in neat packages, and they defy simple attempts at management. Is it any more productive to comprehend the far-reaching revolutions ushered in by silicon chips,[283] or, to go further back in time, petrochemicals and plastics? These component materials have remade society in pervasive and sometimes unexpected ways, and they have forced any number of legal institutions to adapt old strategies to new challenges,[284] but no one now would express surprise or disappointment that regulatory officials or courts initially failed to appreciate these forces or design uniform and coherent (and perhaps counterproductive) responses.

¶ 77 Occasionally, commentators suggest that we find ourselves in the midst of more

281. *See id*. ("Federal agencies including the [FDA, EPA, and OSHA] have acknowledged that current regulations may not adequately protect against nanoparticles' unique toxicities, but those agencies have only recently begun considering how to respond."); Weiss, *supra* note 276, at A2 ("U.S. regulations relating to worker safety, environmental protection, cosmetic sales and drug approvals have not been adapted to address the novel traits of these materials, in part because it has proven difficult to predict which nanomaterials pose risks. But several agencies have begun to conduct safety studies."). Both the FDA and the EPA have begun to focus on these sorts of questions. *See* Andrew Bridges, *After Illness, a Closer Look at Nano Science*, PHILA. INQUIRER, Apr. 14, 2006, at C2 (reporting that the FDA has scheduled a public meeting to discuss safety issues in the wake of an incident in Germany where almost 100 people developed respiratory problems after using an aerosol cleaning product purportedly containing nano-sized particles); Paul Carlstrom, *Nanotech Material Toxicity Debated: More Oversight Being Urged by Environmentalists*, S.F. CHRON., Sept. 12, 2005, at G1; Rick Weiss, *Nanotechnology Regulation Needed, Critics Say*, WASH. POST, Dec. 5, 2005, at A8.

282. *See* Reynolds, *supra* note 11, at 199-201; *id*. at 197 (calling for "a modest form of regulation coupled with robust civilian research – an approach that has been applied successfully to biotechnology"); *id*. at 203 ("The single most successful example of technology control in the last century was the regulatory regime established for biotechnology. . . . [I]t was largely 'soft law,' more the product of professional self-regulation, culture, and expectations than of harsh regulatory systems."); Jason Wejnert, *Regulatory Mechanisms for Molecular Nanotechnology*, 44 JURIMETRICS J. 323 (2004); *see also* Rick Weiss, *Stricter Nanotechnology Laws Are Urged: Report Warns of Risk to Public*, WASH. POST, Jan. 11, 2006, at A2.

283. *See* Patricia Sullivan, *Engineer's Tiny Chip Changed the World*, WASH. POST, June 22, 2005, at A1 (reporting the death of Jack Kilby, "almost 50 years after his idea for what is commonly known as the microchip revolutionized the way that the world computes, calculates and communicates, ushering in the Information Age").

284. *See, e.g.*, Gary M. Hoffman & Geoffrey M. Karny, *Can Justice Keep Pace with Science?*, WASH. POST, Apr. 10, 1988, at B3 (discussing the responses of courts to new challenges presented by emerging computer technologies); *see also* Amy Harmon, *Technology Elite Are Focusing Next on Human Body*, N.Y. TIMES, June 16, 2003, at C1 (reporting forecasts of a revolutionary convergence between medicine and information technology); Annys Shin, *Internet Visionaries Betting on Green Technology Boom*, WASH. POST, Apr. 18, 2006, at D1 (describing these sorts of breakthroughs as "disruptive" technologies).

than just a technological revolution, drawing parallels to profound leaps in the development of civilization such as the Stone Age and the Iron Age.[285] Perhaps in hindsight this transition will deserve equal billing with the likes of such epochs, but in the present we need to take care not to exaggerate the supposed profundity of scientific progress occurring at this moment. Otherwise, society may become excessively enamored with – or frightened by – the latest domain of undoubtedly significant innovation.

¶ 78 Biotechnology has ushered in profound changes at some levels (and may require special attention from regulators),[286] but, in other respects, it has shown remarkable continuity with the techniques that preceded it. As my Torts professor used to ask us in class, though in reference to hypothetical variations of the case law under discussion, "is it a difference that makes a difference?" Legal institutions must try to avoid getting blinded by the hype and inappropriately sweeping in – and perhaps overregulating – both the novel and the mundane applications of this still young science and newer ones just on the horizon.

285. *See* Ashley R. Melson, *Bioterrorism, Biodefense, and Biotechnology in the Military: A Comparative Analysis of Legal and Ethical Issues in the Research, Development, and Use of Biotechnological Products on American and British Soldiers*, 14 ALB. L.J. SCI. & TECH. 497, 498 & n.10 (2004); *id*. at 502 (suggesting that the challenges presented by biotechnology, at least in the military context, surpass those ushered in by the "Information Revolution"); *see also* JEREMY RIFKIN, THE BIOTECH CENTURY: HARNESSING THE GENE AND REMAKING THE WORLD (1998); *cf*. Huhn, *supra* note 40, at 1 ("The Renaissance, the Industrial Revolution and the Information Age each represent a 'great leap forward' in human potential. The Genetic Age promises another exponential increase in human knowledge and potential."); Barbara R. Jasny & Leslie Roberts, *Introduction: Building on the DNA Revolution*, 300 SCIENCE 277 (2003) (special section celebrating the 50th anniversary of the discovery by Watson & Crick); Robert L. King, *The Modern Industrial Revolution: Transgenic Animals and the Patent System*, 67 WASH. U. L.Q. 653 (1989).

286. *See* Cross, *supra* note 59, at 862, 920-24 (suggesting alternatives to the use of the precautionary principle); Sunstein, *supra* note 59, at 1014-18, 1054-58 (recognizing the place for a weak version of the precautionary principle); *see also* John P. Dwyer, *Overregulation*, 15 ECOLOGY L.Q. 719 (1988).