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Regulation of Biotechnology in the European Community: How Twelve Nations Are Transforming a Global Industry

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REGULATION OF BIOTECHNOLOGY IN THE EUROPEAN COMMUNITY: HOW TWELVE NATIONS ARE TRANSFORMING A GLOBAL INDUSTRY

I. INTRODUCTION AND SUMMARY

Biotechnological[1] breakthroughs are expected to improve greatly our quality of life, by providing cures to diseases, enhancing the quantity and nutrition of food, and offering non-chemical alternatives to pollution remediation. Not surprisingly, industry proponents tout biotechnology as the panacea for many basic human problems.[2]

More cautious observers of the industry, however, assert that engi-

1. Biotechnology has been defined as "[t]he application of organisms, biological systems or biological processes to manufacturing and service industries. This definition has been extended to include any process in which organisms, tissues, cells, organelles or isolated enzymes are used to convert biological or other raw materials to products . . . ." J. COOMBS, DICTIONARY OF BIOTECHNOLOGY 41 (1986).

2. *See, e.g.*, ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT, BIOTECHNOLOGY: ECONOMIC AND WIDER IMPACTS 22 (1989).

neering novel organisms could create unanticipated hazards.[3] Those who are wary of lax regulation of biotechnology products note that while knowledge about scientific mechanisms is incomplete, research continues at a breakneck pace.[4] They fear that incomplete assessment of genetically modified organisms could have unforeseen, even disastrous consequences once the organisms or their products reach the consuming public.[5]

Biotechnology has received increased attention by health and safety regulators in recent years. Whereas the trend in the United States has been to ease the regulatory burden,[6] the emphasis in the European Community (E.C.)[7] has been to tighten and harmonize regu-

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3. *See, e.g.*, MARGARET MELLON, NAT'L WILDLIFE FED'N, BIOTECHNOLOGY AND THE ENVIRONMENT 13 (1988) (discussing our inability to predict the effects that releases of genetically modified organisms may have on complex ecological systems).

4. *See, e.g., id.* at 8-9 ("Our understanding about ecological processes simply lags behind our knowledge of molecular processes. And we have almost no practical experience with engineered organisms that have been released into nature.").

5. *See, e.g., id.* at 31-32. For example, *Rolling Stone* magazine writer Tom Curtis suggests that AIDS may have been transmitted to humans through a polio vaccine that had been cultured in monkey cells containing the HIV virus. Tom Curtis, *The Origin of AIDS*, ROLLING STONE, Mar. 19, 1992, at 54, 54. Curtis speculates that the responsible vaccine may have been one that was widely distributed between 1957 and 1960 during a polio immunization campaign in Zaire. *Id.* at 56. Although many have dismissed this story as sensationalist journalism, *see* Carol Saline, *Did Hilary Koprowski Unleash AIDS?*, PHILADELPHIA MAG., May 1992, at 73, 114, the virus was first detected in a human in 1959 in Zaire, Curtis, *supra* at 56, and the controversy persists. Saline, *supra* at 114.

Some fear that this sort of mingling of organic materials among species can produce wholly unanticipated results, such as the transmission of a strain of virus that is innocuous in one species but pathogenic in another, or the transmission of an innocuous strain that mutates into a virulent form. For example, the monkey B virus produces a very mild reaction in monkeys, but can paralyze and kill humans. Curtis, *supra* at 57. Because the risks of this virus were known, monkeys were generally tested for it, and most polio vaccines were not contaminated with the monkey B virus. *Id.*

6. *See, e.g., FDA Head of Biologics Will Accelerate Review Timetable*, BIOTECHNOLOGY NEWSWATCH, Mar. 16, 1992, at 1, 1 (1992).

7. The European Community was established when the Treaty of Rome came into force on January 1, 1958. TREATY ESTABLISHING THE EUROPEAN COMMUNITY [EEC TREATY]. This Treaty, together with the Treaty of Paris (April 1951), TREATY ESTABLISHING THE EUROPEAN COAL AND STEEL COMMUNITY [ECSC TREATY], and a second Treaty of Rome (March 1957), TREATY ESTABLISHING THE EUROPEAN ATOMIC ENERGY COMMUNITY [EURATOM TREATY], formed the Constitution of the European Community. The goal of the Treaty of Rome was to integrate the European market in terms of goods, persons, services and capital. *See* EEC TREATY arts. 2-3 & 8A. Nearly ten years later, on July 1, 1967, the separate councils and commissions of these Communities fused into one. *See generally* EUROPE 1992: AN AMERICAN PERSPECTIVE 1,

latory standards.[8]

One recently proposed regulation in the European Community that concerns marketing authorizations for biotechnology-derived medicinal products is particularly noteworthy.[9] The proposal has been wending its way through the Community's cooperation procedure[10]

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app.1-1 at 51-52 (Gary C. Hufbauer ed., 1990).

8. *See, e.g.*, AUDREY WINTER ET AL., BUREAU OF NAT'L AFFAIRS, EUROPE WITHOUT FRONTIERS: A LAWYER'S GUIDE 272-77 (1989).

9. Amended Commission Proposal for a Council Regulation (EEC) Laying Down Community Provisions for the Authorization and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Agency for the Evaluation of Medicinal Products, 1991 O.J. (C 310) 7 [hereinafter Amended Proposed Regulation].

The regulation will establish a binding, centralized marketing authorization system for biotechnology-derived pharmaceuticals. Commission Proposal for a Council Regulation (EEC) Laying Down Community Procedures for the Authorization and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Agency for the Evaluation of Medicinal Products, 1990 O.J. (C 330) 1, 1 (First recital) [hereinafter Proposed Regulation]. Marketing authorizations will be granted only where a scientific evaluation indicates the product meets quality, safety and efficacy standards. *Id.* (Fourth recital). Although the current system does provide for central review, decisions by the reviewing committee are nonbinding. *See id.* (Second recital). Thus companies wishing to market in the Community must still obtain marketing approval from individual Member States. In contrast, the proposed regulation will permit Community-wide marketing for authorized pharmaceuticals. See *Ministers Set to Approve Central Medicines Agency*, 1 WORLD PHARMACEUTICALS REP., July 20, 1992, at 3, 3-4, for a discussion of the proposal.

10. Proposed legislation is reviewed and revised by various institutions within the E.C. Legislation generally takes the form of a directive (which is only fully implemented through national legislation by each Member State), or a regulation (which is binding on all Member States and does not require national legislation for implementation).

Under the cooperation procedure, the Commission proposes legislation. The Commission is composed of 17 members; all 12 E.C. countries have at least one Commissioner. Following the Commission proposal, the Parliament reads the proposed legislation and issues an advisory opinion. The Parliament is composed of 518 members who are elected directly in each E.C. country. The Council of Ministers then votes on the proposal. Each Member State is represented by a Minister, though Minister votes are weighted according to population and Gross Domestic Product. Unlike participants on most other bodies in the E.C., the Ministers are expected to represent the interests of their Member States, rather than the Community. The Council submits the legislation to the Parliament, which conducts a second reading. If Parliament approves the legislation, it is adopted; if Parliament rejects the legislation, it is sent to the Council of Ministers for a vote. If Parliament amends the legislation, it is submitted to the Commission to redraft and re-propose to the Council, whereupon the Council will vote. In addition to these standardized procedures, the Economic and Social Committee may also submit an advisory opinion to the Commission. See INT'L DIV., U.S. CHAMBER OF COMMERCE, EUROPE 1992: A PRACTICAL GUIDE FOR AMERICAN BUSINESS 18-24 (1989) for a succinct overview of the E.C. legislative procedure.

since 1990, and appears to be nearing official adoption.[11] The most salient element of the proposal is centralization of review,[12] based on specific public health criteria of quality, safety and efficacy.[13] Although it harmonizes Community health standards, this regulation also facilitates the free movement of these biotechnology-derived products throughout the E.C.[14] Nonetheless, health issues dominate the proposed regulation, as evidenced by a statement from its preamble:

> [I]n the interests of public health and the consumers of medicinal products it is necessary that decisions on the authorization of such medicinal products should be based on the objective scientific criteria of the quality, the safety and the efficacy of the medicinal product concerned to the exclusion of economic or other considerations . . . .[15]

Industry response in Europe to this proposed regulation has been cautiously optimistic.[16] Most Community biotechnology organizations and firms seem to believe that harmonization and centralization will improve their ability to market pharmaceuticals once approval is obtained, but they also fear that procuring authorization may result in "administrative juggernaut."[17]

U.S. industries' reaction to the E.C. regulations is less clear. On the one hand, the E.C. proposal will impose regulatory requirements on

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11. The proposed regulation has been drafted and submitted by the Commission, Proposed Regulation, *supra* note 9; reviewed by the Economic and Social Committee, Economic and Social Committee Opinion, 1991 O.J. (C 269) 84; commented upon by the Parliament, Parliament Amended Text, 1991 O.J. (C 183) 145; amended by the Commission, Amended Proposed Regulation, *supra* note 9, at 7; and submitted to the Council of Ministers for a vote. The Council is expected to render its decision before the end of 1992. *See, e.g., EC: Europe Documents; No 1796 - State of Completion of the Single Market (3 of 3)*, Reuter Textline, Agence Europe, Sept. 11, 1992, ¶ 86, *available in* LEXIS, Nexis Library.

12. Proposed Regulation, *supra* note 9, at 1 (Third recital).

13. Amended Proposed Regulation, *supra* note 9, at 1 (Fourth recital).

14. Proposed Regulation, *supra* note 9, at 1 (First recital). The European Community is currently composed of twelve members: France, Germany, Italy, the United Kingdom, Spain, the Netherlands, Belgium, Greece, Portugal, Denmark, Ireland, and Luxembourg.

15. Amended Proposed Regulation, *supra* note 9, at 1 (Fourth recital).

16. *See, e.g.*, Elisabeth Tacey, *Pharmaceuticals: The Route to the Market*, FIN. TIMES, Nov. 21, 1990, at 39.

17. *See id.* The "administrative juggernaut" term originated with an E.C. Commission official, who claimed the harmonized procedure would *not* lead to this result. *Ministers Set to Approve Central Medicines Agency*, *supra* note 9, at 3.

companies that market in the Community. On the other hand, however, companies that meet those standards will gain access to twelve national markets. Thus, these proposed regulations will profoundly improve the ability of international pharmaceutical companies to reach European consumers.

The E.C. proposal contrasts significantly with federal Food and Drug Administration (F.D.A.) laws, regulations and policies. Federal statutes governing pharmaceuticals in the U.S.[18] have not been amended with new provisions addressing biotechnology-derived products.[19] Instead, the F.D.A. generates guidance documents to apprise applicants of recommended procedures.[20] Although the agency updates these documents to keep current with technology and agency concerns, the constantly evolving character of F.D.A. review opens the agency to external pressures, particularly from the White House. Partly pursuant to such Executive Branch influence,[21] the F.D.A. recently promised to simplify and accelerate approval of these products.[22] In essence, approval by the F.D.A. is less predictable and consistent than will be the case in the European Community.

Some U.S. officials and industry representatives have become increasingly critical of burdensome federal health standards, particularly as the biotechnology industry has become more competitive.[23] Although the U.S. leads globally in this technology, its competitive edge is not assured.[24] Consequently, industry proponents have stepped up their ef-

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18. Federal Food, Drug and Cosmetic Act (FFDCA), 21 U.S.C. §§ 301-392 (1988); Public Health Service Act, 42 U.S.C. §§ 262-263n (1988).

19. Food and Drug Administration: Statement of Policy for Regulating Biotechnology Products, 51 Fed. Reg. 23,309, 23,310 (1986).

20. *Id.* at 23,311.

21. *See, e.g.*, Philip J. Hilts, *U.S. Says It Will Speed Gene-Product Approvals*, N.Y. TIMES, Mar. 6, 1992, at D2. [hereinafter *U.S. Says It Will Speed*]; *see also Vice President Dan Quayle, Remarks to the Food and Drug Law Institute Conference re: President's Council on Competitiveness* (Dec. 11, 1991), *in* Federal News Service, Dec. 11, 1991, *available in* LEXIS, Nexis Library.

22. *See, e.g., FDA Head of Biologics Will Accelerate Review Timetable, supra* note 6, at 1.

23. *See, e.g., U.S. Patent Decisions, Federal Regs Loom Large for Biotech Firms*, INDUS. BIOPROCESSING, June 1991, at 2, 2.

24. *See, e.g.*, OFFICE OF TECHNOLOGY ASSESSMENT, BIOTECHNOLOGY IN A GLOBAL ECONOMY 19-21 (1991) (noting the U.S.' general preeminence in the technology, but also Japan's strength in fermentation processes and Europe's strength in pharmaceuticals and agriculture); THE PRESIDENT'S COUNCIL ON COMPETITIVENESS, REPORT ON NATIONAL BIOTECHNOLOGY POLICY 5 (1991) (asserting that Japan and Europe have begun to challenge the U.S.' lead in the industry).

forts to ease the regulatory burden.[25]

Despite the F.D.A.'s recent measures to streamline the biotechnology approval process, adoption of the proposed E.C. regulation will force U.S. drug companies marketing in Europe to meet the more clearly defined Community safety and efficacy standards.[26] Because of keen competition in this industry, U.S. companies hoping to maintain their current strength must elect to meet stringent E.C. public health and scientific criteria. Their ability to reach European markets will require it. Additionally, because all countries (including biotechnology strongholds Japan and Switzerland) will also experience pressure to comply with these comprehensive standards, no country will endure an unfair disadvantage. The worldwide effect of this E.C. Commission proposal will be improved health and safety for the public, as well as increased access to important markets for the biotechnology industry.

This Note explores the far-reaching impact of this proposal, particularly with reference to the United States. Section II examines sev-

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25. For example, the industry has been involved actively with President Bush's Council on Competitiveness and its anti-regulatory agenda. The Council strives to maintain and improve U.S. competitiveness by developing human resources, promoting technological progress, removing "barriers to innovation," assessing "governmentally-imposed burdens on the free enterprise system," and removing "domestic barriers to the flow of goods and services." THE PRESIDENT'S COUNCIL ON COMPETITIVENESS, *supra* note 24, at 25. The association between industry and the Council is so close, in fact, that House Energy and Commerce/Health Committee Chair Waxman (D-Calif.) has begun to investigate alleged improper ties between Eli Lilly and Company and the Council. *See Rep. Waxman Investigating Quayle Council Proposals for FDA Drug Approvals; Possible Hearing Angles are Lilly Influence and Intra-Agency Reservations*, 53 F-D-C REP. 15-16 (1991). Evidence of Lilly's extensive ties to the Council include President Bush's former membership on Lilly's board of directors, Vice President Quayle's prior representation as a senator of this Indiana constituent, Lilly Vice President Mitchell Daniel's political directorship in Reagan's administration, and Lilly's technical assistance with Council on Competitiveness proposals. *Id.*

In addition, trade groups such as the Industrial Biotechnology Association acknowledge that the Council has requested their help in preventing Congress from cutting the Council's funding. *See Bush to Biotechs: Save COC from Congress*, BIOTECHNOLOGY NEWSWATCH, Sept. 7, 1992, at 12 (1992). Senator John Glenn (D-Ohio) has threatened to take measures to eliminate the Council's funding, alleging "[T]he council carries out its agenda under a shroud of secrecy—a shroud that is only lifted to grant access to certain special interests." *Id.*

26. Before U.S. products can be marketed in the E.C. they must receive marketing authorization pursuant to Article 3 from the Proposed Regulation. ("No medicinal product which is [developed by a biotechnological process] shall be placed on the market within the Community unless authorization has been granted by the Community in accordance with the provisions of this Regulation." Proposed Regulation, *supra* note 9, art. 3, at 3.)

eral key elements of the proposed regulation, following a brief look at previous Community regulations. Section III discusses industry's response to the proposal, both in Europe and the United States. Section IV contrasts the E.C. proposal with current U.S. laws and policies. Finally, Section V concludes that this proposal will have what many consider an almost inconceivable effect: benefits for both public welfare and American industry.

II. THE EUROPEAN COMMUNITY PROPOSED REGULATION AUTHORIZING MARKETING OF BIOTECHNOLOGY DRUGS

Beginning in 1975, the European Community operated under a marketing system in which individual Member States were responsible for upholding Community standards of safety, quality and efficacy.[27] Member States granted marketing authorizations, though States could consult the E.C. Committee for Proprietary Medicinal Products (CPMP) for non-binding opinions about authorization refusals, authorization suspensions or non-compliance with authorizations.[28]

The CPMP review procedures were modified in Council Directive 87/22 eleven years later for several reasons, including the following:

> 1) the provisions "[we]re not sufficient to open up to high-technology medicinal products the large Community-wide single market they require,"[29]
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> 2) "the scientific expertise available to each of the national authorities [wa]s not always sufficient to resolve problems posed by high-technology medicinal products,"[30]
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> 3) it was necessary to unify Community decisionmaking by "provid[ing] for a Community mechanism for concertation, prior to any national decision relating to a high-technology me-

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27. Second Council Directive 75/319 on the Approximation of Provisions Laid Down by Law, Regulation or Administration Action Relating to Proprietary Medicinal Products, art. 4, 1975 O.J. (L 147) 13, 14, amended by Council Directive 83/570, 1983 O.J. (L 332) 1, 9, last amended by Council Directive 89/381, 1989 O.J. (L 181) 44, 45. Article 4 standards in Directive 75/319 are those enumerated in Council Directive 65/65 on the Approximation of Provisions Laid Down by Law, Regulation or Administration Action Relating to Proprietary Medicinal Products, 1965 O.J. (L 22) 369.

28. Second Council Directive 75/319, art. 8(2), 1975 O.J. (L 147) 13, 15; *see also supra* note 9.

29. Council Directive 87/22 on the Approximation of National Measures Relating to the Placing on the Market of High-Technology Medicinal Products, Particularly Those Derived from Biotechnology, 1987 O.J. (L 15) 38, 38 (Fifth recital).

30. *Id.* (Sixth recital).

dicinal product,"[31] and

4) there was a "need for the adoption of new technical rules applying to high-technology medicinal products . . . so as not to endanger the advance of pharmaceutical research whilst at the same time ensuring optimum protection of public health within the Community."[32]

In essence, the new Directive 87/22 required Member States to refer biotechnology marketing applications to the CPMP for an opinion before the State could award a marketing authorization.[33] Although Committee review became mandatory under this Directive, Member States were still entitled to reach their own decisions, and merely notified the Committee of their ultimate conclusions.[34]

Dissatisfaction with Directive 87/22 led to the most recent regulatory proposal,[35] the Proposal for a Council Regulation (EEC) Laying Down Community Provisions for the Authorization and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Agency for the Evaluation of Medicinal Products, which calls for centralization of marketing authorizations for biotechnology-derived pharmaceuticals.[36] Such authorizations, the Commission now believes, should be granted "only after a single scientific evaluation of the highest possible quality of all the benefits and risks of technologically advanced medicinal products, . . . by a rapid procedure ensuring close cooperation between the Commission and Member States."[37]

A. A Single Scientific Evaluation of the Highest Possible Quality

The single scientific evaluation will be undertaken by a newly established agency, entitled the European Agency for the Evaluation of

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31. *Id.* (Seventh recital).
32. *Id.* (Ninth recital).
33. *Id.* arts. 1-2(2), at 38-39.
34. *Id.* art. 4(4), at 40.
35. Proposed Regulation, *supra* note 9, at 1 (Third recital); *see also EC Proposes Centralized Regulation of Pharmaceuticals*, The Reuter Library Rep., Oct. 19, 1990, *available in* LEXIS, Nexis Library ("In the majority of Community countries, the authorisation systems are in crisis, paralysed by criticism from consumer groups and by the number and complexity of cases to examine," while "[t]he absence of a credible authorisation system valid throughout the Community is penalising its pharmaceutical industry, including its exports." *Id.* (quoting a statement from the E.C. Commission)).
36. Proposed Regulation, *supra* note 9, at 1.
37. *Id.* at 2 (Eighth recital).

Medicinal Products (Agency).[38] The Agency coordinates the scientific review of the product for quality, safety and efficacy and presents reports and summaries of its findings.[39]

The CPMP, under the Agency's supervision, reviews documentation submitted by an expert for the applicant, certifying that the product received specific testing for harmfulness and efficacy, as required by Council Directive 75/318.[40] Directive 75/318, as amended by Commission Directive 91/507, requires testing to be state-of-the-art and validated.[41] Directive 91/507 also mandates documentation of chemical, pharmaceutical, toxicological and clinical testing, and specifies the necessary elements of those experiments.[42]

B. Risks

The Agency must examine and balance both consumer and environmental risks created by a new product.[43] Most consumer risks are studied and documented during quality, safety and efficacy testing, pursuant to Directive 75/318, as amended.[44] Environmental risks, however, constitute a new element in the risk-benefit analysis for

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38. *Id.* arts. 47-48, at 12.

39. *Id.* art. 48(a)-(b), at 12.

40. *Id.* art. 6, at 3, citing Council Directive 75/319, art. 2, 1975 O.J. (L 147) at 14, which refers to Council Directive 75/318 on the Approximation of the Laws of Member States Relating to Analytical, Pharmacotoxicological and Clinical Standards and Protocols in Respect of the Testing of Proprietary Medicinal Products, 1975 O.J. (L 147) 1, amended by Council Directive 89/341, 1989 O.J. (L 142) 11, modified by Commission Directive 91/507, 1991 O.J. (L 270) 32.

41. Commission Directive 91/507, Annex, 1991 O.J. (L 270) 32, 36. ("All the test procedures shall correspond to the state of scientific progress at the time and shall be validated procedures; results of the validation studies shall be provided.").

42. *Id.* at 36-52.

43. Proposed Regulation, *supra* note 9, at 2 (Seventeenth recital) (describing the need for "intensive monitoring of adverse [clinical] reactions to those medicinal products through Community pharmacovigilance activities in order to ensure the rapid withdrawal from the market of any medicinal product which presents an unacceptable level of risk under normal conditions of use"); Amended Proposed Regulation, *supra* note 9, at 8 (Twentieth recital) (describing the need "to provide for an environmental risk assessment of [medicinal products containing or consisting of genetically modified organisms]").

44. Commission Directive 91/507, Annex, 1991 O.J. (L 270) at 34-52. Commission Directive 91/507 most recently amended Council Directive 75/318 by replacing the Annex to Directive 75/318. The Annex outlines the types of tests and data that must be submitted in an application for a marketing authorization. Under the new Annex "Chemical, Pharmaceutical and Biological," "Toxicological and Pharmacological" and "Clinical" tests are required. Commission Directive 91/507, Annex, 1991 O.J. (L 270) at 36-52.

pharmaceuticals. Risks associated with intentional releases of genetically modified organisms into the environment (as in agricultural applications) have received increased attention in the E.C., culminating in Council Directive 90/220.[45] The Amended Proposed Regulation has adopted some of the provisions from Directive 90/220.[46] Specifically, the Amended Proposal requires each biotechnology pharmaceutical application to include "a copy of the written consent, from the competent authority, to the deliberate release of the genetically modified organisms for research and development purposes," and a "complete technical dossier supplying the information requested in Annexes II and III of Directive 90/220 [characterizing the organisms, the release and the environment] and the environmental risk assessment resulting from this information."[47]

Though the Amended Proposed Regulation adopts some environmental risk provisions from Directive 90/220, it does not adopt others. Article 6(2) of the Amended Proposed Regulation, codifying environmental requirements, states that Articles 11 through 18 of Directive 90/220 do not apply to the Amended Proposed Regulation.[48] Those provisions pertain to the release of genetically modified organisms as products.[49] Consequently, it appears that the environmental risk assessment required under the Amended Proposed Regulation concerns only releases into the environment pursuant to research and development, not releases in the form of marketable goods.[50]

There are two problems with this apparent import of the Amended Proposed Regulation. First, it is impractical in application, because it is difficult to conceive of the need for any deliberate release into the environment of a pharmaceutical product during research and development. In contrast with, for example, agricultural applications of biotechnology products, medical applications of biotechnology products would not involve deliberate environmental releases. Second, the Amended Pro-

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45. Council Directive 90/220 on the Deliberate Release into the Environment of Genetically Modified Organisms, 1990 O.J. (L 117) 15 (requiring, among other things, a case-by-case environmental risk assessment prior to any release of genetically modified organisms into the environment. *Id.* (Ninth recital)).

46. The Amended Proposed Regulation adopts Article 2(1) & (2), Article 6(4), and Annexes II and III from Council Directive 90/220. Amended Proposed Regulation, *supra* note 9, art. 6(2) & (4), at 8-9.

47. Amended Proposed Regulation, *supra* note 9, art. 6(2), at 8-9.

48. *Id.* at 9.

49. Council Directive 90/220, arts. 11-18, 1990 O.J. (L 117) 18-20.

50. Note also that Article 6(4) from Directive 90/220 falls under Part B of the Directive, entitled, "Deliberate release of GMOs into the environment for research and development purposes or any other purpose than for placing in the market." *Id.* at 18.

posed Regulation is unsound as a matter of policy in that it ignores potential environmental releases from use of the product itself. Use of a biotechnology-derived product by definition introduces an organism into the human environment, which would almost certainly introduce it into the greater environment. Inadvertent (but foreseeable) spillage of drugs, discarding of partially used containers, or release of organisms through human bodily fluids, such as blood or urine, would all introduce organisms into the environment. Deliberate use should be seen as synonymous with deliberate release, and should warrant an environmental risk assessment. Unfortunately, the Amended Proposed Regulation does not apply Directive 90/220 in such a fashion, and fails to require an environmental assessment of risk from the use of biotechnology-derived products.

C. Rapid Procedure

The Proposed Regulation ensures rapid processing of applications by requiring quick turn-around at all stages of the procedure. For example, the initial authorization opinion must be rendered by the Committee for Proprietary Medicinal Products (CPMP) (under supervision of the European Agency for the Evaluation of Medicinal Products) within 210 days after the CPMP receives an application.[51] If, however, the CPMP requests supplementation of the application, or if the applicant prepares oral or written explanations at the CPMP's request, then this time limit will be temporarily suspended.[52] Once the initial opinion is issued, the applicant has only fifteen days in which to notify the Agency of an appeal.[53] The CPMP, in turn, must make its final determination within sixty days of the appeal.[54] The supervisory Agency forwards the CPMP's final opinion with a report containing Committee comments to the E.C. Commission, Member States and the applicant within thirty days.[55]

Within thirty days of obtaining the CPMP opinion, the Commission prepares its draft Decision, which it transmits to the Member States and the applicant.[56] The Commission adopts the Decision within thirty days unless "it has received a reasoned request from a Member

51. Amended Proposed Regulation, *supra* note 9, art. 6(4), at 9.
52. Proposed Regulation, *supra* note 9, art. 7(c), at 3-4.
53. *Id.* art. 9(1), at 4.
54. *Id.*
55. *Id.* art. 9(2), at 4.
56. Amended Proposed Regulation, *supra* note 9, art. 10(1), at 9.

State to reconsider."[57] If such a request is received, the Commission reassesses its decision, provided the request is based on scientific evidence or Community law.[58] In the absence of any delays, authorizations may be approved as quickly as 300 days after an application is submitted. It is difficult to conceive of a more condensed timetable, given the complex, multi-stage procedure.[59]

D. Close Cooperation

The Proposed Regulation provides for close cooperation between the Commission and Member States through a number of means. As indicated above, the various E.C. organs of the reviewing process communicate frequently with the applicant and Member States. The Proposal also delineates cooperative networks between the Agency and the Member States. For example, both the Agency and Member States must assist with the collection and review of pharmacovigilance information.[60] Member States are expected to notify the Agency of relevant information about adverse reactions to authorized medicinal products, and the Agency is responsible for collecting and evaluating this information.[61] The Proposal also delegates some authority to Member States. For example, it designates Member States as official "supervisory authorities"[62] to assure that manufacturers or importers are complying with their authorization decisions, as provided by Directive 75/319.[63]

The Proposed Regulation also includes provisions requiring the Commission to respond to Member States' concerns. Thus if a Member State informs the Commission that it believes a manufacturer or importer is not fulfilling its Directive 75/319 obligations,[64] the Commis-

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57. *Id.* art. 10(2), at 10.

58. *Id.*

59. Marketing authorizations now take more than a year in the European countries, according to Bruce Merchant, chairperson of the Association of Biotechnology Companies. *See Biotech Approval Process Criticized by the Industry*, CHEMICAL MARKETING REP., Nov. 19, 1990, at 4, 4. Of course, approval in one country does not guarantee approval in another, under the current national approval system in the E.C.

60. Proposed Regulation, *supra* note 9, arts. 19-25, at 6-7. Pharmacovigilance involves "the collection and evaluation of information about adverse reactions to medicinal products." *Id.* art. 20, at 6.

61. *Id.*

62. Proposed Regulation, *supra* note 9, art. 16, at 5.

63. *Id. See also id.* art. 17(1), at 6, referencing Chapters IV and V of Council Directive 75/319. These Chapters define the supervisory authorities' necessary qualifications and the extent of their duties.

64. Amended Proposed Regulation, *supra* note 9, art. 18(1), at 12.

sion must review the matter and render a Decision.[65] Similarly, where a Member State makes a "reasoned request"[66] for an inspection of a manufacturing site, the Commission may order such an investigation.[67] The Proposal even permits Member States to act on their own initiative, for example, "where action is urgently necessary to protect public health."[68] This element of cooperation should assure smoother approvals and better enforcement of the regulations.

III. INDUSTRY'S RESPONSE

A. Europe

E.C. industries have rated inconsistent technical regulations as the most significant trade barrier within the Community.[69] Of all industries adversely affected by technical barriers, European businesses rank the pharmaceutical sector the fourth most hindered industry.[70] The industries have also specifically blamed inconsistent technical standards for creating expensive delays during certification and registration of pharmaceuticals.[71] Under the former national registration system, for example, approval took up to three years in Italy and Spain, and up to two years in Germany and the United Kingdom.[72]

Although E.C. businesses seem to believe that harmonization of regulations for pharmaceutical authorizations is desirable, praise for the Proposed Regulation is qualified. One British industry representa-

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65. Proposed Regulation, *supra* note 9, art. 18(2)-(3), at 6.

66. *Id.* art. 17(2), at 6.

67. *Id.*

68. Amended Proposed Regulation, *supra* note 9, art. 18(4), at 12. Member States may act without consulting the Commission in the following scenarios: (1) where harm that could be caused would be so severe that the State cannot await a Commission decision, (2) where it is likely that the suspected harm will occur during Commission review, or (3) where the harm posed by the product outweighs the risk to patients currently taking the medicinal product from removing the product from the market. *Id.* art. 18(4)(1)-(3), at 12.

69. MICHAEL EMERSON ET AL., THE ECONOMICS OF 1992: THE E.C. COMMISSION'S ASSESSMENT OF THE ECONOMIC EFFECTS OF COMPLETING THE INTERNAL MARKET 39 (1988). This conclusion was based on a 1987 study undertaken by G. Nerb, Directorate-General for Economic and Financial Affairs, Commission of the European Communities, entitled *The Completion of the Internal Market: A Survey of European Industry's Perception of the Likely Effects.*

70. PAOLO CECCHINI ET AL., THE EUROPEAN CHALLENGE 1992: THE BENEFITS OF A SINGLE MARKET 27, tbl. 4.1 (J. Robinson ed., 1988). This data was also gleaned from the G. Nerb survey, mentioned *supra* note 69.

71. EMERSON, *supra* note 69, at 44.

72. *Id.* at 73.

tive, for example, has remarked: "Intellectually we think they're going down the right track, but the potential for bureaucratic nightmare is high."[73] Some European companies not only fear complex procedures, but also voice concern about national biases among members on the Committee for Proprietary Medicinal Products and the CPMP's advisory Scientific Committee.[74] Although the Proposed Regulation requires independent scientists to staff the CPMP,[75] European businesses would like assurances that those experts are both highly competent and impartial.[76] The mood in Europe seems to be guarded optimism.

B. United States

The U.S. Chamber of Commerce describes the general E.C. harmonization process as "potentially a double-edged sword for U.S. business."[77] On the positive side, harmonization will mean that U.S. companies need meet only one set of standards in order to market in all E.C. member countries. However, those companies will operate at a disadvantage if the U.S. is not included in the standard-setting process, if U.S. testing and certifying entities are not recognized by central E.C. agencies, or if the standards require expensive adjustments by American companies.[78]

The U.S. National Association of Manufacturers (NAM) believes that the "establishment of a new E.C.-wide standards process may af-

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73. Tacey, *supra* note 16, at 39 (quoting Frances Charlesworth of the Association of the British Pharmaceutical Industry).

74. *See id.* The Committee for Proprietary Medicinal Products (CPMP) is currently composed of representatives of national agencies. The proposed regulation theoretically will limit nationalistic tendencies by replacing these representatives with independent scientific experts. *See id.*

In a recent meeting of the Council of Ministers, the Commission presented several recommendations for facilitating neutral review by the Scientific Committee, which advises the CPMP. First, Scientific Committee members should represent the Member States that appointed them. Second, Member States should not give those scientists instructions that conflict with their committee obligations. Third, the Committee should select rapporteurs to evaluate applications on behalf of the committee, not Member States, and rapporteurs should coordinate the reviews. *EC: Progress Towards Single Market in Medicines at Council Meeting*, Reuter Textline, Agence Europe, July 7, 1992, *available in* LEXIS, Nexis Library. These three recommendations would accommodate the dual need for Member State representation as well as independent scientific reviews.

75. Proposed Regulation, *supra* note 9, art. 50(1), at 13.

76. *See, e.g.*, Tacey, *supra* note 16, at 39.

77. INT'L DIV., U.S. CHAMBER OF COMMERCE, *supra* note 10, at 45.

78. *See id.*

fect more U.S. companies than any other EC-92[79] issue."[80] In addition, NAM notes that, while the intent of such harmonization is not to open E.C. markets to non-E.C. companies, non-E.C. companies stand to benefit when they successfully receive clearance from one authority and thus gain access to all E.C. markets.[81] NAM concludes that "*[i]n principle, the adoption of common standards is widely seen by U.S. companies in Europe as a major benefit.*"[82]

Representatives from the National Bureau of Standards, however, note that E.C.-wide standards may unintentionally restrict market access for U.S. goods.[83] The Bureau reiterates the warning of the Chamber of Commerce that denying U.S. companies an early opportunity to review and comment on E.C. proposals increases the likelihood that later U.S. comments will not receive full consideration,[84] as well as the possibility that the resulting standards may be unfavorable to them.[85]

Although the U.S. apparently had little input in formulating the proposed E.C. regulation, federal regulators, industry representatives, and scientists are encouraged by their recent discussions with E.C. regulators about harmonization of pharmaceutical registration procedures.[86] These parties attended an international conference on pharmaceuticals,[87] which laid to rest some of the primary concerns of

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79. "EC-92" refers to the anticipated completion of the European Common Market and removal of all intra-E.C. trade barriers by 1992. In 1985 the E.C. Commission drafted a document entitled, *Completing the Internal Market: White Paper from the Commission to the European Council* (Luxembourg, 1985), which sets forth the unification plan. *See* STEPHEN COONEY, NAT'L ASSOC. OF MANUFACTURERS, EC-92 AND U.S. INDUSTRY 9-12 (1989).

80. COONEY, *supra* note 79, at 15.

81. *Id.*

82. *Id.* at 17.

83. Patrick W. Cooke & Donald R. Mackay, *The New EC Approach to Harmonization of Standards and Certification*, BUS. AM., Aug. 1, 1988, *reprinted in* COONEY, *supra* note 79, at 49 app. The U.S. Chamber of Commerce notes that the E.C. could also deliberately adopt standards that would be incompatible with U.S. goods, in order to attain a competitive advantage. INT'L DIV., U.S. CHAMBER OF COMMERCE, *supra* note 10, at 47.

84. Cooke & Mackay, *supra* note 83, *in* COONEY, *supra* note 79, at 49.

85. *Id.*

86. *See* THE FIRST INTERNATIONAL CONFERENCE ON HARMONISATION, PRESS RELEASE (Nov. 8, 1991), *reprinted in* INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE, at 5 (1991).

87. Over 1200 people attended the conference. Participants included the Commission of the European Communities, the U.S. Food and Drug Administration, the Japanese Ministry of Health and Welfare, the International Federation of Pharmaceutical Manufacturers Associations, the European Federation of Pharmaceutical Industry As-

the Chamber of Commerce. For example, the participating regulatory agencies agreed to accept certain data evaluations from each other in order to promote efficiency and to control costs.[88] The consensus of this meeting and of numerous businesspersons seems to be that harmonization will be beneficial in the long run, if somewhat painful in the short term.

IV. U.S. REGULATIONS AND POLICIES TOWARDS APPROVAL OF BIOTECHNOLOGY PHARMACEUTICALS

In contrast to the proposed E.C. regulatory framework, the federal regulatory landscape is a bit more haphazard. Federal policies concerning approval of drugs for the U.S. market are neither simple nor fixed. Moreover, U.S. laws do not apply readily to biotechnology products because the laws have not been altered to reflect the peculiarities of those goods.[89] In contrast, the E.C.'s proposed regulation directly addresses public health concerns about biotechnology products. Rather than modifying its regulations, the F.D.A. has instead adopted various policies pertaining to biotechnology drug approvals.[90] For example, the agency

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sociations, the U.S. Pharmaceutical Manufacturers Association and the Japanese Pharmaceutical Manufacturers Association. *Id.*

88. *See id.* The point of this principle is to avoid unnecessary duplication of testing to comply with the varying standards of different regulatory agencies.

89. 51 Fed. Reg. 23,309, 23,310 (1986). The F.D.A. concedes "there are no statutory provisions or regulations that address biotechnology specifically . . . ." *Id.* Nonetheless, the agency maintains that existing laws and rules suffice and that agency personnel can capably administer them. ("[T]he laws and regulations under which the agency approves products place the burden of proof of safety as well as effectiveness on the manufacturer. The agency possesses extensive expertise with these regulatory mechanisms and applies them to the products of biotechnological processes.").

90. The F.D.A. has described these documents as "guidance to current or prospective manufacturers of drugs and biological products . . . describing points that manufacturers might wish to consider in the production and testing of products." 51 Fed. Reg. at 23,311 (1986). Although these documents instruct the applicants, because they are not binding they do not promote regulatory consistency. F.D.A. comments in a recent Federal Register notice suggest that the approval process is becoming even more ambiguous:

> The supplement [to this points to consider document] has been developed to revise and update information in a previously issued points to consider (PTC) document in order to improve the document's usefulness; *it is neither a regulation nor a guideline, but represents the current thinking* of the [F.D.A.] Center for Biologics Evaluation and Research (CBER).
>
> . . . A manufacturer may choose to use alternative procedures even though they are not described in the PTC and this PTC supplement. A manufacturer who wishes to use other procedures is encouraged to discuss the matter with the agency.

recommends certain testing procedures in periodic "Points to Consider" documents,[91] and has announced its intent to conduct case-by-case review.[92]

A. A Single Scientific Evaluation of the Highest Possible Quality

The F.D.A. also implements the four broad principles of the E.C. proposal somewhat differently. As the sole federal agency empowered to approve drugs, it does, however, conduct a single scientific evaluation. Although the F.D.A. oversees all review, different types of biotechnology materials are approved by separate divisions of the agency. "Biological products,"[93] for example, are licensed for marketing by the Center for Biologics Evaluation and Research.[94] "New drugs,"[95] mean-

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Notice, 57 Fed. Reg. 33,201, 33,202 (1992) (emphasis added).

91. 51 Fed. Reg. at 23,311 (1986).

92. *Id.*

93. "Biological product," or biologic, means "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound)." Public Health Service Act, 42 U.S.C. § 262(a) (1988).

94. The Center for Biologics Evaluation and Research (CBER) licenses both biologic products and establishments that manufacture those products. 21 C.F.R. § 601.4(a) (1992). Because the products are organic and may contain elusive contaminants such as viruses or natural toxins, biologics review is highly complex. Consequently, the CBER reviews the manufacturing process carefully for flaws. Telephone Interview with Steve Falter, Director of the Division of Regulations and Bioresearch Monitoring, Center for Biologics Evaluation and Research, Food and Drug Administration (Oct. 16, 1992) [hereinafter Telephone Interview with Falter].

95. "New drug" is defined as a drug "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective." Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 321(p)(1) (1988).

"Drugs" are defined as articles intended for diagnosing, curing, mitigating, treating, preventing disease, or affecting the structure or function of the body. 21 U.S.C. § 321(g)(1) (1988).

Manufacturers of drugs that are not "new," but generally recognized as safe and effective (GRASE), need not submit new drug applications. Arguably, biotechnology-derived versions of GRASE drugs (previously approved and manufactured using conventional processes) should be exempt from the new drug approval process. Historically, however, the F.D.A. has considered all biotechnology-derived drugs as "new." *See* Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology, letter from Elaine C. Esber, M.D., Director, Office of Biologics Research and Review, Food and Drug Administration, to Manufacturers of Recombinant DNA Products and other Interested Parties at 3 (Apr. 10, 1985) [hereinafter Points to Consider, letter from Esber] ("New license applications or new drug applications are required before marketing products made with recombinant DNA technology, even if the active ingredient in the product is thought to

while, receive marketing approval from the Center for Drug Evaluation and Research.[96] Despite this branched approach, the reviews of biologics and new drugs are "functionally very similar."[97] The agency has jurisdiction over both forms of pharmaceuticals and thus its review remains centralized.

Arguably, however, the F.D.A. procedure fails to ensure review of the highest possible quality. The reason for this appears to be the absence of mandated research and testing standards. For example, the F.D.A. recommends that biotechnology companies seeking federal approval follow the rigorous National Institutes of Health Guidelines for

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be identical in molecular structure to a naturally occurring substance or a previously approved product produced in an established manner." Points to Consider documents can be obtained from the F.D.A. by writing to the Congressional and Public Affairs Staff at the agency.) In a fairly recent policy statement, F.D.A. repeated its "general principle, [that] new marketing applications will be required for most products manufactured using new biotechnology." 51 Fed. Reg. 23,309 (1986). Importantly, however, the agency qualified this maxim: "[E]ach case will be examined separately to determine the appropriate information to be submitted. In some instances new applications may not be required." *Id.*

96. In contrast to the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research approves only products, not establishments. In this sense the application for new drugs requires less data than one for biologicals. *See* Robert A. Swanson, *Culturing a Biotech Company in a Regulatory Medium*, *in* DRUG BIOTECHNOLOGY REGULATION: SCIENTIFIC BASIS AND PRACTICES 382, 385 (Yuan-yuan H. Chiu & John L. Gueriguian eds., 1991).

However, unlike biologic licensee applicants, new drug applicants must undertake multiple, carefully controlled human studies that demonstrate the drug's effectiveness. *See* Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 617-18 (1973) (concluding that a showing of efficacy for a new drug includes evidence of adequate and well-controlled clinical studies). Although the Supreme Court has found that the Federal Food, Drug and Cosmetic Act requires these sorts of human trials, it has never found them necessary under the Public Health Service Act, governing biologicals. Telephone Interview with Falter, *supra* note 94.

As one might expect, because the requirements for biologics and new drugs vary slightly, pharmaceutical companies might prefer one label over the other. For example, an applicant would be spared scrutiny of its manufacturing process if the product received the "new drug" label. (Note that the Federal Food, Drug and Cosmetic Act authorizes the F.D.A. to enter and inspect any manufacturing establishments. 21 U.S.C. § 374(a) (1988). These inspections are not tied to the approval process, however.) On the other hand, an applicant would be relieved from conducting extensive drug efficacy trials in humans if the product were deemed a "biological product." The F.D.A. determines whether a product falls into one category or the other. Understandably, characterization is often difficult. Many biotechnology products are reviewed as biologics.

97. Telephone Interview with Falter, *supra* note 94.

Research Involving Recombinant DNA Molecules,[98] but goes no further.[99] The N.I.H. Guidelines, themselves, technically apply only to federally funded projects.[100] In addition, because the agency publishes advisory "Points to Consider" documents for biotechnology products, rather than issuing legally binding regulations, it cannot guarantee consistency among biotechnology applicants.[101]

Although these policies provide the flexibility necessary to respond to rapidly changing technology, they also expose the agency to outside pressures. For example, the Executive Branch has taken a keen interest in promoting biotechnology, expressing its intent to "oppose any efforts to create or modify existing regulatory structures for biotechnology through legislation."[102] A recent announcement from the administration's Office of Science and Technology Policy (OSTP) reflects this anti-regulatory agenda.[103] The OSTP declared that, "within the scope of discretion afforded by statute [oversight] should not turn on the fact that an organism has been modified or modified by a particular process or technique, because such fact is not alone a sufficient indication of risk."[104]

This policy runs counter to current F.D.A. practice, at least with respect to biotechnology drugs. The agency treats these drugs as "new,"[105] which means applicants must submit a lengthy application and reams of scientific data. It is soundly within agency discretion to

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98. National Institutes of Health: Guidelines for Research Involving Recombinant DNA Molecules, 51 Fed. Reg. 16,958 (1986). The first version of this document was published in 1976. 41 Fed. Reg. 27,906 (1976). Among other things, the Guidelines restrict certain types of experiments, define levels of physical and biological containment, establish containment levels according to level of risks, and define the roles of the various participants. *See* Gregory A. Jaffe, *Inadequacies in the Federal Regulation of Biotechnology*, 11 HARV. ENVTL. L. REV. 491, 498 (1987).

99. *See* Points to Consider, letter from Esber, *supra* note 95, at 3. The Points to Consider document mentions that there may be other applicable guidelines for importers, e.g., from the World Health Organization. *Id.*

100. 51 Fed. Reg. 16,958, 16,965 (1986). Because, according to one estimate, more than 90% of all recombinant DNA research is privately funded, the N.I.H. Guidelines may have little impact on most research, particularly commercial research. *See* Jaffe, *supra* note 98, at 534.

101. *See supra* note 90.

102. THE PRESIDENT'S COUNCIL ON COMPETITIVENESS, *supra* note 24, at 14.

103. Office of Science and Technology Policy: Exercise of Federal Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment, 57 Fed. Reg. 6753 (1992).

104. *Id.* at 6756.

105. *See supra* note 95.

treat biotechnology-derived drugs as either "new" or GRASE,[106] where the product had been previously approved using conventional techniques. Consequently, this OSTP policy may radically alter F.D.A. review practices.

B. Risks

Similar to the CPMP, the F.D.A. does conduct a risk analysis. Consumer risks are subsumed in the general review, but environmental risks are evaluated somewhat differently. The National Environmental Policy Act (NEPA),[107] which requires an environmental impact assessment for all "major Federal actions significantly affecting the quality of the human environment,"[108] applies to all premarketing approvals by the agency.[109] Although the F.D.A. believes that most new products only require submission of a brief environmental assessment,[110] a lengthy environmental impact statement is necessary for products that may cause significant environmental impacts.[111] Because risk assessments under the Federal Food, Drug and Cosmetic Act are not limited to research and development risks, as under the proposed E.C. regulations, review of environmental risks may be more thorough in the United States than in the European Community.

C. Rapid Procedure

Like its European counterparts, the F.D.A. has been unable to achieve rapid procedure. Agency approval has been very slow, largely due to understaffing.[112] According to the Pharmaceutical Manufactur-

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106. Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 627 (1973).

107. National Environmental Policy Act, 42 U.S.C. §§ 4321-4364 (1988).

108. *Id.* § 4332(C).

109. 51 Fed. Reg. 23,309, 23,313 (1986). *See also* 21 C.F.R. § 25.22(a)(14) & (16) (1992) (requiring submission of an environmental assessment when seeking approval for new drugs and licensing of biological products).

110. 51 Fed. Reg. 23,313 (1986) ("For new products or major new uses for existing products, these [NEPA-implementing] procedures ordinarily require the preparation of an environmental assessment.").

111. *Id.* ("An environmental impact statement is required if the manufacture, use, or disposal of the product is anticipated to cause significant environmental impacts.").

112. *See, e.g., U.S. Says It Will Speed, supra* note 21, at D2. Approval in the U.S. averages 32 months for new drugs, though approval of biotechnology-derived new drugs generally requires only half of the time. OFFICE OF TECHNOLOGY ASSESSMENT, *supra* note 24, at 90. The Office of Technology Assessment concludes that drug approval is often slower in the United States than in the rest of the world. *Id.*

See also Biotech Approval Process Criticized by the Industry, supra note 59, at 4

ers Association, for example, only two biotechnology products were approved last year, while twenty-one awaited approval and over 130 were undergoing review.[113] Overall, the agency approved thirty new drugs and eight biologics in 1991 (including both biotechnology-derived and conventional products).[114] To improve its sluggish pace, the agency recently announced plans to hire fifty new scientists to review biotechnology applications.[115] One senior official from the agency indicated the F.D.A.'s intention "not [to] be obstructionist" and to "keep our standards but . . . [to] make things move."[116]

Congress passed a unique piece of legislation in the waning hours of the 102d Congress in an attempt to fund and expedite F.D.A. review.[117] The "Prescription Drug User Fee Act of 1992" aims to cut review time in half.[118] It will raise $300,000,000 by the close of 1997, allowing the agency to hire 600 additional examiners.[119] Under this Act, pharmaceutical companies will pay the F.D.A. $100,000 per drug (or biologic) application, $50,000 per year and at least $6,000 per drug on the market. In five years those fees will increase to $233,000, $138,000 and $14,000, respectively.[120] Congress secured industry's support because approval delays cost companies more than user fees: every month approval is delayed translates into $10,000,000 of lost profits.[121] Moreover, Congress ensured the backing of pharmaceutical firms by

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(citing ABC chairperson Bruce Merchant's estimate of 34 months for biotechnology-derived biologic licensing approvals); *FDA Approves 30 Drugs in 1991 in Average of 30.3 Months*, WORLD PHARMACEUTICAL STANDARDS REV., Mar. 1992, at 9, 9 (citing the Pharmaceutical Manufacturers Association's estimate of 30.3 months for new drug approvals) [hereinafter *FDA Approves*]; *Drugs, User Fee System is Essential for FDA to Keep Pace with NDAs, Kessler Says*, DAILY REP. for EXECUTIVES (BNA) No. 155, at A9, A9 (Aug. 11, 1992) (citing F.D.A. Commissioner Kessler's recent estimate that approval of new drugs takes 20 months, while approval of breakthrough drugs takes 12 months). "Breakthrough" drugs treat serious illnesses for which there are no cures, such as AIDS, cancer or Alzheimer's disease. *See* Alex Barnum, *FDA Speeding up Drug Testing; Outside Contractors Will Help Review Applications in Some Cases*, THE S.F. CHRONICLE, Apr. 10, 1992, at A9.

113. *See FDA Approves*, *supra* note 112, at 9.

114. *See id.*

115. *See, e.g.*, *U.S. Says It Will Speed*, *supra* note 21, at D2.

116. *Id.*

117. Prescription Drug User Fee Act of 1992, H.R. 6181, 102d Cong., 2d Sess. (1992).

118. Philip J. Hilts, *Senate Passes Bill to Charge Makers for Drug Approval*, N.Y. TIMES, Oct. 8, 1992, at A1.

119. *Id.*

120. *Id.* at B25.

121. *Id.* at A1.

convincing them that the fees would benefit the review process directly.[122]

D. Close Cooperation

Regulation in the U.S. does not require the cooperation of sovereign Member States, as in the European Community. Although individual U.S. states may regulate biotechnology,[123] regulation in the U.S. is almost entirely federal. Thus, harmonization of state laws is essentially a non-issue. Close coordination between the agency and applicants, on the other hand, raises certain conflict-of-interest issues.

Arguably, active dialogue between the applicant and the F.D.A. clarifies and hastens the approval process. Ostensibly towards this end, the agency has expressed its intent to be "user-friendly."[124] However, the F.D.A. has been criticized for its ties to industry, and has been labeled the "Chamber of Commerce" of biotechnology.[125] Importantly, it should not be forgotten that F.D.A.'s central legal obligation is to protect the public from dangerous foods, drugs, and cosmetics.[126] The appropriate amount of interaction between the F.D.A. and industry is clearly debatable; the recent federal policy, however, has been to strengthen and expand government and industry collaborations.[127] As

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122. *Id.* at B25.

123. State and local regulation is rare, however. For a discussion of some state and local regulations, *see* Diane Hoffman, *The Biotechnology Revolution and its Regulatory Evolution*, 38 DRAKE L. REV. 471, 537-39 (1988-1989). Note, for example, that Maryland enacted a statute in 1977, requiring all researchers to comply with the N.I.H. Guidelines. This Maryland statute expired in 1982. Recombinant DNA Research, ch. 847, 1977 Md. Laws 3305.

124. BUREAU OF NATIONAL AFFAIRS, U.S. BIOTECHNOLOGY: A LEGISLATIVE AND REGULATORY ROADMAP 21 (1989) (quoting former F.D.A. Commissioner Frank Young) [hereinafter U.S. BIOTECHNOLOGY].

125. *Id.* at 27. Andrew Kimbrell, policy director for Jerry Rifkin's public interest group, the Foundation on Economic Trends, is credited with this characterization. He claims that the F.D.A. acts "as a promoter [of biotechnology] rather than a regulatory agency." *Id.* (alteration in original).

126. *See* 62 Cases, More or Less, Each Containing Six Jars of Jam v. United States, 340 U.S. 593 (1950), which held:

> The purposes of this [FFDCA] legislation, we have said, "touch phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection. Regard for these purposes should infuse construction of the legislation if it is to be treated as a working instrument of government and not merely as a collection of English words."

Id. at 596 (quoting United States v. Dotterweich, 320 U.S. 277, 280 (1943)).

127. Government collaboration, or assistance that tends to strengthen ties between the public and private sector, includes research funding and tax reform, as well as

long as policymakers believe that public and private sector cooperation improve the U.S.' competitive edge, we can probably expect to see this trend continue.

In summary, F.D.A. review is less standardized and less rule-bound than the proposed E.C. process. As indicated above, the recent tendency has been to relax those malleable F.D.A. policies further. The trend towards deregulation of biotechnology products seems clear in this country. Consequently, the reverse trend in the E.C. may have a striking effect.

V. THE E.C. REGULATION AND ITS EFFECT ON THE BIOTECHNOLOGY INDUSTRY

The importance of the biotechnology industry to the U.S. economy cannot be overemphasized.[128] It remains one of the few industries in

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industry and government research collaborations.

The U.S. is clearly committed to providing financial assistance for biotechnology research. *See* THE PRESIDENT'S COUNCIL ON COMPETITIVENESS, *supra* note 24, at 6. According to the President's Council, the U.S. invested $3.5 billion in biotechnology-related research in fiscal year 1990. *Id.* The Office of Technology Assessment estimates that the government funds over half of all biotechnology-related research in the United States. OFFICE OF TECHNOLOGY ASSESSMENT, *supra* note 24, at 163.

Tax credits for biotechnology companies may be particularly helpful to spur industry growth, because biotechnology requires an inordinate amount of investment in research and development. *See* OFFICE OF TECHNOLOGY ASSESSMENT, *supra* note 24, at 64. American biotechnology companies benefit from several such tax credits. *See id.* at 64-66 for a discussion of available U.S. tax breaks.

Although on a small scale only, the government has formed several collaborative arrangements with industry. For example, the F.D.A. plans to establish a National Center for Toxicological Research, in Arkansas, and to rent a portion of its space and equipment to start-up biotechnology firms short on capital. *See* U.S. BIOTECHNOLOGY, *supra* note 124, at 26.

128. Biotechnology is considered an industry of great importance for the present as well as the future. Its importance has been equated with the computer industry. *See* JOHN NAISBITT & PATRICIA ABURDENE, MEGATRENDS 2000, at 260 (1990). In addition, because the U.S. leads in research and commercialization of biotechnology, American industry proponents see the industry as presenting a golden opportunity for the U.S. economy.

Growth in the U.S. has been rapid. In the last four years, development of biotechnology-derived pharmaceuticals has increased by 60% in the United States, according to a survey by the Pharmaceutical Manufacturers Association. *See USA: Biotech Drugs; Research in the US and Europe*, Reuter Textline, Chemical Business News Base, May 29, 1992, *available in* LEXIS, Nexis Library. Moreover, since 1983, the number of jobs has increased 10-fold, from 5,000 to 50,000. *Biotechnology Research to Receive Increased Funding, National Commitment, According to U.S. Report*, WORLD PHARMACEUTICAL STANDARDS REV., Mar. 1990, at 13, 13 (citing comments from For-

which the U.S. is the most technically advanced. The U.S. also boasts close ties between industry and academia,[129] which should ensure continued development in the future. If these strengths can be exploited commercially, it is possible that the industry will become "the automobile industry of the future."[130] It is easy to understand why regulators have begun to succumb to economic pressures.

Success in this industry requires not only a solid research base, however, but the ability to reach global markets. International marketing has already begun: over one third of all drugs sold in the Community are imported, mostly from the U.S. and Switzerland.[131] Moreover, the European market is crucial to American biotechnology pharmaceutical companies; biotechnology products are still extremely expensive to produce, due to astronomical research and development costs.[132] Broad-based marketing is clearly important for companies seeking to recoup their costs.

Marketing in the E.C. is also appealing to U.S. corporations because entry into one country will mean immediate entry into eleven others. Because marketing in Europe is so desirable, it appears that U.S. biotechnology pharmaceutical companies will feel compelled to comply with the proposed E.C. regulation. The paradox of this otherwise burdensome regulation is that compliance with it will enhance the ability of U.S. companies to compete. The incentive to comply will be great. Although U.S. regulators are showing neither the conviction nor the interest in imposing strict public health and quality standards, the E.C. has, and for once, both the public and industry stand to gain.

Colleen K. Ottoson

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rest Anthony, president of the Association of Biotechnology Companies, during a January 29, 1992 press conference). The industry has not even experienced a decline during the current economic recession, with sales in 1991 approaching $4 billion. *Id.* Finally, the U.S. trade balance is also healthy, with exports exceeding imports. *Id.*

129. *See, e.g.*, ORGANIZATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT, BIOTECHNOLOGY AND THE CHANGING ROLE OF GOVERNMENT 39 (1988).

130. *Biotechnology: Draft of Long-Awaited 'Scope' Document Calls for Risk-Based Regulatory Approach*, DAILY REP. FOR EXECUTIVES (BNA) No. 36, at A-4 (Feb. 24, 1992) (quoting William Small, Executive Director of the Association of Biotechnology Companies).

131. *See, e.g.*, EMERSON, *supra* note 69, at 71.

132. *See, e.g.*, BUREAU OF NATIONAL AFFAIRS, THE BIOTECH BUSINESS: FINANCIAL OUTLOOK AND ANALYSIS 7-23 (1989). For example, research and development expenses can reach $45,000 per employee. *Id.* at 18.