Chapter 16

Health, Safety, and Environmental Regulation

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Introduction

Regulation has been and will continue to be a factor in the development of biotechnology, especially for recombinant DNA (rDNA) processes and products. When the rDNA technique was first developed, its novelty and tremendous power to manipulate organisms raised the specter of potentially drastic consequences to human health and the environment through the creation and proliferation of organisms with unknown but potentially hazardous traits. In the United States, therefore, Congress moved to develop stringent regulation of rDNA. This movement was forestalled in part by the adoption in 1976 of fairly restrictive self-regulatory guidelines by the scientists (27).

As time passed, however, concern and fears diminished greatly. As scientists learned more about molecular genetics, perceived risks associated with probing the unknown diminished, and no evidence was discovered to support many of the early risk scenarios. Formal risk assessment studies also led to downward evaluation of potential risk. Molecular biologists gained the confidence of the public by bringing other experts and the public into the decisionmaking process that established the system of voluntary self-regulation. And, most importantly, there has been no evidence of any harm to human health or the environment from rDNA. Consequently, the requirements of the rDNA guidelines in the United States have been substantially relaxed.

Today, most experts believe that the potential risks of rDNA research were drastically overstated and that rDNA technology generally does not involve a risk beyond that already inherent in the host, vector, DNA, solvents, and physical apparatus being used (35). This is not to say, however, that biotechnology-like most new technologies-does not continue to raise special concerns or present special risks. In particular, questions have been raised about the long-term effects on workers' health from exposure to novel organisms and products and about the risks of deliberately releasing genetically manipulated organisms into the environment. In addition, some of the products that will be made by biotechnology may present special risks. For example, the U.S. Food and Drug Administration (FDA) has been concerned about bacterial endotoxins found in drugs produced by ***Escherichia coli*** **(28).**

Regulation will have a moderately important effect on the development of biotechnology and, consequently, on U.S. competitiveness in biotechnology. Special risks may lead to limited new regulation that could direct commercial efforts away from certain areas or at least slow advancements in those areas. In addition, most of the products that could be made by biotechnology and associated processes are already subject to considerable regulation, pharmaceuticals and chemicals being the best examples. This existing regulation also will affect corporate strategies and patterns of industrial development.

The costs and time involved in complying with regulatory requirements are the price society pays for safety. However, unreasonable restrictions and unnecessary burdens may delay or prevent important products from reaching the market or may increase the business risks of developing those products. Uncertainties, for example, about what the regulatory requirements will be or which agencies have jurisdiction, will also affect the risk, time, and cost of product development. Those countries that have the most favorable regulatory environment in terms of least restrictions and uncertainties will have a competitive advantage in the commercialization of biotechnology.

This chapter evaluates the regulatory environment for the commercialization of biotechnology in the United States and five competitor countries

being examined in this assessment—the Federal Republic of Germany, the United Kingdom, France, Switzerland, and Japan. Two specific factors are considered in the evaluation: 1) the restrictiveness of the regulation, and 2) the uncertainties with respect to possible agency jurisdiction or requirements. Congressional options for improving U.S. competitiveness in biotechnology through changes in the regulatory environment are presented at the end of the chapter.

In the analysis that follows four areas of regulation are considered:

- regulation directed specifically toward biotechnology;
- existing regulation that would apply to biotechnology products;
- environmental regulation relevant to biotechnology; and
- worker health and safety regulation.

The chapter concentrates on the guidelines for rDNA research adopted by the competitor countries and the approval requirements for pharmaceuticals (human drugs and biologics) and for veterinary medicines (animal drugs and biologic). The guidelines for rDNA research merit significant attention because they are the only type of governmental oversight developed specifically for biotechnology. The approval requirements for pharmaceuticals and veterinary medicines also merit attention because those products are subject to the most restrictive regulation, even when made by conventional means, * and because so much of the current activity in biotechnology is directed toward those types of products. In addition, with respect to regulation of products in other countries, most of the information OTA was able to obtain related to the approval process for pharmaceuticals and veterinary medicines. Sufficient information on foreign regulation of food, food additives, medical devices, and chemicals was not available for meaningful international comparisons; however, this information is included for the United States because of its availability and because of the interest in it.

Two inherent limitations could qualify the analysis in this chapter. The first results from the difficulty of determining and interpreting foreign laws and especially the rules and policies of the foreign agencies. Much of this material is not readily available in English or even in the native language. In addition, enforcement of laws and regulations in other countries generally is much more discretionary than in the United States. * Thus, there may be a wide gap between the written laws and regulations and the actual regulatory environment in which foreign companies operate. The second limitation results from the fact that the analysis does not consider the positive effects of regulation and a country's track record for safety. In other words, the restrictiveness of regulation theoretically should be balanced against some measure of the harm avoided. However, the necessary data are generally not available, and such an analysis is beyond the scope of the chapter,

*"Significant regulation also exists for commodity and specialty chemicals (including herbicides and pesticides), but it is generally not as restrictive as for pharmaceuticals and some types of veterinary medicines. The use of genetically modified organisms in the environment will probably face some moderate degree of regulation, Agricultural products currently face little health, safety, or environmental regulation, but this situation could change in the case of genetically modified plants and animals.

*In fart, this discretion has led to claims of selective enforcement against U.S. companies, thus creating a nontariff trade barrier, For discussion of other nontariff trade barriers, see ***Chapter 19: International Technology Transfer, Investment, and Trade.***

Regulation directed specifically toward biotechnology: rDNA research guidelines

The only oversight mechanism directed specifically toward biotechnology is the rDNA research guidelines. These guidelines grew out of the concerns in the mid-1970's about potential risks of rDNA research and the desire to proceed cautiously in the face of the uncertainties. Guidelines

similar to the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) in the United States have been adopted by Japan, the Federal Republic of Germany, the United Kingdom, France and Switzerland. Over time, they have been substantially relaxed worldwide in a series of revisions that reflect decreasing concern about the risk. In fact, many types of experiments involving rDNA are now exempt from the guidelines. The guidelines are essentially self-regulatory.

The guidelines for rDNA research reflect the decision by experts and policymakers that rDNA research presents some special risks and uncertainties that require special attention. They are based on two underlying concepts:

- rDhA research should be conducted at increasing levels of physical and biological containment related to the degree of possible hazard, and
- the degree of oversight should relate to the degree of possibIe hazard.

The implementation of these concepts is fairly similar in the competitor countries, because the worldwide scientific community was involved in their development and because most countries followed the lead of the United States. Nevertheless, there are some important differences among the guidelines adopted in the various countries, and different countries are at different stages in the process of relaxing them.

This section surveys the rDNA research guidelines of the six competitor countries with respect to their scope, containment requirements, approval requirements, and enforcement mechanisms in order to assess their impact on competitiveness in biotechnology. * The commercial development of biotechnology in many of these countries, however, will depend less on the specific biological and physical containment measures required by their rDNA research guidelines than on the scope of activities reached by the guidelines (i.e., whether they cover large-scale research) and the structure set up for implementing and enforcing the guidelines. The analysis presented here is based on the more detailed description of the rDNA research guidelines of the six countries and the European Economic Community found in ***Appendix F: Recombinant DNA Research Guidelines, Environmental Laws, and Regulation of Worker Health and Safety,*** which the reader is urged to examine.

*Provisions relating specifically to worker health and safety are discussed in the section of this chapter entitled "Regulation of Worker Health and Safety."

Scope

In the United States, Japan, and France, the guidelines technically apply only to government-funded rDNA research, while in Switzerland, the Federal Republic of Germany, and the United Kingdom, they apply to all rDNA research. (Actually, all the guidelines also apply to large-scale rDNA work to varying degrees, as discussed below.) While U. S., Japanese, and French private laboratories might seem to have some advantage over private laboratories in the other countries because they could dispense with safety measures perceived to be unnecessary, this '(advantage" is probably illusory, Industry perceives compliance with the guidelines to be in its best interest, and there has been no publicized evidence of noncompliance.

Perhaps the single most important issue for companies using biotechnology is the rDNA guidelines' treatment of large-scale research (i.e., work with cell cultures in volumes exceeding 10 or 20 liters), which is a necessary step in successful commercial development. The guidelines in Japan are easily the least favorable in this regard. Recombinant DNA research with volumes exceeding 20 liters can be conducted in Japan only after Government permission, and that permission has been quite difficult to obtain. * It should be noted, however, the situation in Japan is expected to change shortly. * * Under the U.S. guidelines, the large-scale work need only be reviewed by each

● Six companies have obtained permission for large-scale work (14),

• *The Council for Science and Technology, which advises the Prime Minister and oversees rDNA work by private institutions in Japan, is expected to recommend the elimination of the prohibition of large-scale work without special Government approval. Instead, large-scale bioprocess facilities would classify into two categories, LS1 and LS2. LS1 facilities would be covered by rules similar to those for conventional microbiological laboratories, LS2 facilities, which would involve work with more hazardous micro-organisms, would be covered by more stringent rules. The Prime Minister is expected to act favorably on the recommendation in August 1983.

Institutional Biosafety Committee (IBC), although NIH has made specific recommendations regarding physical containment, which were recently incorporated into the U.S. guidelines. Large-scale research in the United Kingdom is treated on a case-by-case basis by the supervising authority, the Genetic Manipulation Advisory Group (GMAG). * But in explaining the need for a different kind of review of large-scale research, GMAG has suggested that large-scale research will not be subject to as stringent containment measures as smaller scale research. The French rDNA guidelines exclude large-scale research from their coverage, but the Government oversight agency will apparently consider such activity on a case-by-case basis. The West German guidelines do not mention large-scale research. The Swiss guidelines permit scaling-up without special approval; it is unclear whether the small-scale rules continue to apply or whether, as with the NIH guidelines, large-scale research is subject to the safety measures decided on by the IBC.

Containment requirements

Each country's rDNA guidelines specify requirements for physical and biological containment of the research organisms. Except for the United Kingdom, each country assesses risk in the same manner—according to the source of the DNA used in the experiment and the pathogenicity of the host-vector system. The United Kingdom determines risk by considering the survivability and likely harm of the organism containing rDNA. Whether this risk assessment method gives the United Kingdom an advantage or disadvantage depends on the particular experiment. The United Kingdom does have an advantage with respect to rDNA production of insulin and interferon, which are classified at a lower containment level there than in the United States (8). Each country uses four levels of physical containment, Most research is now conducted at the lowest physical containment level.

The physical and biological containment measures required for an experiment vary slightly from country to country, but it is difficult to determine what effect on a country's competitive position any one requirement might have. It is difficult to determine, for example, what effect will come from the fact that at the United Kingdom's physical containment level II, a continuous air flow into the laboratory is required, while it is not required in other countries until the third containment level. The measures with the great - est impact are probably the biological containment rules in Japan, which severely restrict the types of organisms that can be used in host-vector systems. These restrictions may prevent commercially promising rDNA research from going forward.

Approval requirements

Notice and approval requirements depend on the risk of the experiment. Research in the United States at the highest risk level is subject to the approval of NIH and the appropriate IBC; at the next level, only IBC approval before initiation is necessary. IBC notification at the time of initiation is required for some lower level risk experiments, while many are exempt entirely. More than 85 percent of all rDNA work in the United States is done at the lowest containment levels (23), and virtually all monitoring of rDNA work is done by IBCS.

The recommendation of the European Economic Community (EEC) on rDNA research suggests that notice of experiments be given to the central authority in each member state, usually before the work begins. For some types of research, notice would not have to be made before work is begun. The United Kingdom, France, and the Federal Republic of Germany are members of the EEC.

In the United Kingdom, the Health and Safety Executive (HSE) is directed to inspect the facilities for rDNA research at the two higher containment levels, categories III and IV. For research at these levels, GMAG also must have notice and an opportunity to give advice. Advance notice is required for research at the category II level but not approval. Activities at the category I level can go forward provided only that the local safety com -

*GMAG's status was recently reviewed by the Health and Safety Executive, and the subsequent report recommended relocation of the group from the Department of Education and Science to the Department of Health and Social Security. GMAG has been moved and is now called the Health and Safety Commission Advisory Group on Genetic Manipulation.

mittee notifies the central authorities once a year of new research. Companies in the United Kingdom also have to deal with two separate agencies: GMAG, which promulgates and monitors the rules, and the HSE, which enforces them.

Scientists in France must notify the French Control Commission (Commission de Contrôle) of planned research. This commission must approve certain high-risk research. Local safety committees monitor the research.

In the Federal Republic of Germany, the Central Commission for Biological Safety (Zentrale Kommission für die Biologische Sicherheit) must be notified of all research except that at the lowest level of containment. This requirement makes for one of the most restrictive approval processes in the countries surveyed. Experiments at the two high-risk levels require the entire commission's approval, while those at the second lowest containment level must be approved by one or two individual members of the commission. The Commission for Biological Safety must also authorize the use of host-vector systems not enumerated in the rDNA research guidelines and may approve reductions in levels of containment employed.

Switzerland, where rDNA research is now conducted under guidelines that are essentially equivalent to the April 1982 NIH Guidelines (34), differs from the United States in an important respect. The research is overseen by a commission created by the Swiss Academy of Medical Sciences. The commission, as a private entity, may be more willing than NIH to modify requirements for projects with which it is familiar.

In Japan, two different bodies monitor rDNA research, the Council for Science and Technology, which supervises activities by private institutions, and the Science Council (in the Ministry of Education), which monitors the activities of public institutions such as universities. The Science Council is not required to approve university experiments, which may go forward simply on the approval of the president of the university and the university safety committee. However, it must approve the use of hosts other than those specified in the guidelines. Only a limited number of hosts and vectors have been approved for use, which puts Japan at a competitive disadvantage.

Enforcement

In all of the countries except the United Kingdom, the only direct sanction for noncompliance with the rDNA research guidelines is the ability of the government to restrict or withdraw funding for an institution's or a scientist's rDNA research. The guidelines in the United Kingdom are promulgated under the Health and Safety at Work Act of 1974 and are backed-up by the general legal sanctions created by that act.

Effect on competitiveness

The commercial effect of the rDNA research guidelines is difficult to assess, because their effect depends on the specific research done and because commercial exploitation of rDNA research has only recently begun. With the exception of Japan and possibly the Federal Republic of Germany, no country's rDNA research guidelines place it in a noticeably disadvantageous position. However, the U.S. rDNA research guidelines are probably the least restrictive of the six competitor countries. The European countries and Japan have generally followed the U.S. guidelines but are often following earlier, more restrictive versions.

Existing regulation of biotechnology products

A comparative assessment of the regulation of biotechnology products in the competitor countries involves two stages. Since biotechnology products generally will be subject to existing regulation for generic products, it is first necessary to compare these general regulatory regimes. In other words, biotechnologically made pharmaceuticals, for example, will be subject to

the general regulations covering pharmaceuticals, regardless of how they are made; thus, comparing the pharmaceutical laws of the different countries will provide information about competitiveness. In this context, the following questions are particularly relevant:

- How much time and effort does it take to get products through the approval process?
- What is the usual or average cost for securing regulatory approvals?
- What are the import and export restrictions on approved and unapproved products?
- Will the regulatory authorities accept foreign test data in the approval process?

The second stage of the analysis involves looking at specific issues raised by biotechnology. Some of these are the following:

- Will new biotechnology products chemically identical to approved products made by other means still be required to go through the full regulatory review process?
- Will the classification of a pharmaceutical as a drug or biologic affect the time or cost of securing regulatory approval?

United States

Three Federal agencies will be most involved in regulating biotechnology products. They are the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and the Environmental Protection Agency (EPA).

FOOD AND DRUG ADM1N1STRATION

FDA regulates drugs, biologics, food, food additives, and diagnostics pursuant to the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. \f301-392) and section 351 of the Public Health Service Act (21 U.S.C. f262).

Since the first commercial applications of biotechnology (i.e., pharmaceuticals) have been in areas subject to FDA jurisdiction, FDA is the agency having the most experience with biotechnology products. FDA has approached rDNA-produced products on an agencywide basis by creating a Recombinant DNA Coordinating Committee, composed of representatives of its centers and bureaus, the office of General Counsel, and Office of Regulatory Affairs. FDA's Recombinant DNA Coordinating Committee has determined that rDNA products whose active ingredients are identical to ones already approved or to natural substances will still have to go through the new product approval process. Data requirements may be modified and often abbreviated, however, and each case will be handled on an ad hoc basis. * (In the case of many conventionally produced products, abbreviated review procedures are available when the active ingredient of the new product is identical to one already approved or to natural substances.) FDA will not require compliance with the NIH Guidelines as a condition of approval. For monoclinal antibody (MAb) products, no coordinating body similar to the Recombinant DNA Coordinating Committee exists; FDA's policy for these products has been set by the National Center for Devices and Radiologic Health (NCDRH) and the Office of Biologics. Actual product regulation will occur at the individual bureaus or offices as discussed below.

Human Drugs.—FDA's Office of New Drug Evaluation has taken the position that drugs made by rDNA technology, even if identical to currently approved drugs, are "new drugs."* * Therefore, such drugs cannot be marketed until approved by FDA as safe and effective.

FDA's approval process for a new drug can take several years because it requires a series of animal and human tests. Clinical investigations can be carried on only after a drug's sponsor files a Notice of Claimed Investigational Exemption for a New Drug (IND). The IND contains the results of animal testing, a description of the planned clinical investigations, and other information. The preclinical investigations generally last from 1 to 2 years (20). The human studies then go through

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"FDA has been concerned about bacterial endotoxins and immunogens contaminating the products and about the genetic stability of the rDNA organism. In the latter case, the product might be affected if the DNA underwent changes.

* ● A new drug is a drug whose composition is not generally recognized by qualified experts as safe and effective under the conditions of use set forth in its labeling or, even if so recognized, has not been used to a material extent or for a material time (sec. 201(p) of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. $321(p)). A drug is a substance intended for use in the diagnosis, treatment, or prevention of disease or which is intended to affect the structure or function of the body (sec. 201(g) of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. $321(g)).

three phases to establish safety, set dosage levels, and establish efficacy. This clinical testing often takes 5 to 6 years (20), During or after the clinical studies, the sponsor files a New Drug Application (NDA), which contains the results of animal and human testing, a statement of the drug's composition, a description of the methods and controls used in its manufacture, and other information. The time required for processing an NDA depends on the completeness of the data, the drug's performance, and the speed of FDA review. In 1980, the duration of the NDA phase for new chemical entities varied from about 1 to 7 years and averaged slightly less than 3 years (20). * Taking into account the research and development (R&D) costs of drugs that fail to reach the market, various economic analyses indicate that the R&D costs per marketed new chemical entity range from $54 million to over $70 million (11).

There are abbreviated approval procedures that FDA might eventually permit sponsors to use after it gains more familiarity with rDNA technology and if warranted by the risks. One is the Supplemental New Drug Application (SNDA), which is required when an NDA holder intends to market the drug under conditions materially different from those approved in the NDA. An SNDA could become available in the case where the manufacturer of an approved drug made by chemical synthesis decides to make the drug by using rDNA and bioprocess techniques. A second procedure is the Abbreviated New Drug Application (ANDA), which is available for generic versions of drugs first marketed between 1938 and 1962. An ANDA might be used by a manufacturer using rDNA techniques to make an approved drug made by conventional techniques by another manufacturer. The final procedure is a "paper" NDA, available for generic copies of drugs marketed after 1962. Such drugs require an NDA, but FDA is willing to accept published reports demonstrating safety and efficacy, thus saving the new sponsor the time and costs of clinical trials. A "paper" NDA could become available in the case where a manufacturer wants to make an rDNA-produced drug whose NDA is held by another manufacturer, if adequate data are available in the published literature to establish safety and effectiveness.

Human Biologics.—A biologic is a vaccine, therapeutic serum, toxin, antitoxin, or analogous product for the prevention, treatment, or care of diseases or injuries, The distinction between a drug and a biologic is largely historical and bureaucratic and is becoming even more blurred with the advent of biotechnology.

Although biologics also come within the definition of drugs in section 201(g) of the Federal Food, Drug, and Cosmetic Act (FFDCA), they primarily are regulated under section 351 of the Public Health Service Act and by FDA's Office of Biologics rather than the Office of **New** Drug Evaluation. * Section 351 creates a regulatory structure for biologics similar to that for drugs. However, it is a licensing procedure; both the product and the establishment where it is produced must be licensed. At the investigational stage, the Office of Biologics follows the requirements for INDs. After clinical trials, the procedure involves a license application for the establishment and for the product; together they provide essentially the same information as required by an NDA. Differences, however, occur in practice. The Office of Biologics generally has been perceived to be more flexible than the Office of New Drug Evaluation. It often uses informal, unpublished guidelines, or "regulatory memoranda ." * * on the other hand, it is the administrative practice of the Office of Biologics to require lot by lot approval of many biologics before they are released by the manufacturer, which is not usually required by the Office of New Drug Evaluation (l).

Biologics made by biotechnology will have to go through the approval process outlined above. In accordance with announced policy, rDNA-pro - duced biologics, even if chemically identical to approved biologics, will have to go through the

*A General Accounting Office study of the U.S. drug approval process found that for 132 NDAs submitted to FDA in 1975, the average approval time was about 20 months (20).

*The Office of Biologics also regulates diagnostics related to blood bank products. All other diagnostics, including most of those incorporating monoclinal antibodies (MAbs), are regulated by FDA's National Center for Drugs and Radiologic Health (NCDRH) The first MAb diagnostic kits related to blood products and were approved by the office of Biologics.

•"It has published three about biotechnology. One covers MAb diagnostic kits for blood bank related products (31) Another covers MAbs for use in human therapy (33). A third covers the production and testing of interferon (32).

full approval process, but data requirements may be lessened. For MAbs, there has been no announced policy, but virtually all of those that would be used for therapeutic purposes would be truly new and therefore have to go through the full review process.

Medical Devices.—Medical devices are regulated by FDA's National Center for Devices and Radiologic Health (NCDRH), except for those in vitro diagnostic products used in connection with blood banking activities such as tests for hepatitis B surface antigen. Those products are regulated by the Office of Biologics.

The Medical Device Amendments to FFDCA in May 1976 required that all devices for human use marketed before the amendments be classified by FDA into one of three categories on the basis of recommendations by expert panels. Class I products are subject to general controls, such as good manufacturing practice regulations. Class II devices are required to meet performance standards in addition to the general controls. Class 111 devices require FDA premarket approval for safety and effectiveness. For devices marketed after May 1976, those that are "substantially equivalent" to a preamendment device are classified with that product, and those that are not substantially equivalent are placed in Class III. Under section 510(k) of the act, manufacturers are required to give FDA a 90-day notice before they can market a device, during which period FDA determines whether the device is substantially equivalent to a preamendment device.

Manufacturers of MAb diagnostic kits generally have been successful in using the 510(k) notice procedure to get their products to the market quickly. Although MAbs are different from and generally superior to polyclonal antibodies for diagnostic purposes, applicants have been successful in showing that MAbs are "substantially equivalent" to polyclonal antibodies marketed before May 1976. That is, the applicants have demonstrated to the satisfaction of NCDRH that the MAbs provide essentially the same (or better) results as polyclonal antibodies used for the same diagnostic purposes (1). Since the review panels of experts required by the statute have placed most preamendment diagnostic kits in Class H (l), the new MAb kits have been placed in Class II, which requires certain performance standards to be met, rather than Class III, which would require the manufacturer to demonstrate safety and efficacy. * The availability of the 510(k) application is highly desirable from a company's perspective because NCDRH must respond within 90 days.

Food and Food Ingredients. •● —The distinction between food and food ingredients (substances added to food) is important in terms of the regulatory approval process. Food can be marketed without FDA clearance, but food ingredients are subject to the food additives provisions of FFDCA, which may require premarketing approval. FFDCA defines food broadly and circularly as food or any component thereof (sec. 201(f)). A food additive is defined as a substance that may, by its intended use, become a component of food or affect the characteristics of food (sec. 201(s)). This definition excludes, among other things, substances generally recognized as safe (GRAS) by qualified experts and certain prior-sanctioned (previously approved) substances. A new food additive requires premarketing clearance by FDA, and its sponsor has the burden of demonstrating its safety. Favorable action by FDA results in a published regulation stipulating the concentration and other conditions under which the additive may be used. GRAS substances technically can be marketed without prior approval by FDA, but also can be the subject of published FDA regulations. * * *

FDA's Bureau of Foods has not been confronted with any foods, food additives, or GRAS substances produced by rDNA techniques; however, on the basis of the announced policy of FDA's Recombinant DNA Coordinating Committee and discussions with the staff, the Bureau appears likely to take the following positions. If FDA were concerned about the safety of such a food, high lysine corn, for example, it could take various

*If a MAb kit were placed in Class 111, the sponsor could petition for a reclassification to Class 11; however, such reclassifications are supposedly difficult to obtain.

* ● This section uses the term food ingredient instead of the term food additive used in other chapters, because the term food additive has a particular meaning under FFDCA. As explained in this section, under FFDCA a food additive is one type of food ingredient (substance added to food).

•• "FDA publishes lists of what it considered to be GRAS substances and sometimes it will consider a substance GRAS only when used under certain conditions.

steps to prevent its sale or remove it from the market by proving it was "ordinarily . . . injurious to health" and, therefore, was adulterated within the meaning of section 402(a) of FFDCA. It might be able to require premarketing clearance if the corn were used as an ingredient in other foods, such as stew, because then it would be subject to the food additive requirements (21 C.F.R. \170.30 (f)), Recombinant DNA products that are similar or chemically identical to GRAS substances or food additives already approved for use will be required to go through the approval process by FDA's Bureau of Foods, although the Bureau will be flexible on data requirements.

Animal Feeds, Feed Additives, and Devices.—These products are regulated in a way similar to the way in which human foods, food additives, and medical devices are regulated; however, the regulation for animal products is less rigorous than that for human products. For animal feeds and feed additives, the requirements for demonstrating safety are less than for the comparable case of human food and food additives. In the case of animal feed additives, however, there is an additional requirement that they be shown to be safe to people consuming edible products from animals receiving the additive. For animal devices, there is no premarket approval requirement as there is for many human devices. At this time, there is no reason to expect any particular regulatory problems if these products are made by biotechnology.

Veterinary Medicines.—For veterinary medicines (animal drugs and biologic), FDA's authority is similar to its authority for human drugs or biologics with two exceptions. First, there is an additional requirement in the animal drug approval process, i.e., animal drugs must not leave unsafe residues or metabolizes in edible tissues or other food products. Second, FDA does not have the primary regulatory authority over animal biologics; USDA regulates them under the Virus, Serum, Toxin Act of **1913** (VST Act) (21 U.S.C. \~151-158), even though they are also technically drugs under FFDCA. USDA's authority applies only to interstate marketing. According to a recent case, FDA has jurisdiction over intrastate marketing (10).

These jurisdictional distinctions have been blurred by rDNA and MAb technology. An FDAAJSDA memorandum of understanding creates a standing committee to sort out regulatory responsibilities in this area (29). * The memo says FDA will regulate where the VST Act does not apply or does not offer an appropriate remedy.

The first product to be considered by the standing committee is bovine interferon. Both agencies claimed jurisdiction, and the committee has split along agency lines. Several attempts to resolve the impasse on scientific grounds have failed; however, efforts are continuing. In the meantime, the manufacturer has encountered additional costs and burdens by attempting to meet the requirements of both agencies (6).

Control Over Exports.—Under section 801(d) of FFDCA, unapproved food additives and medical devices can be exported if certain conditions are met. * * Unapproved new human drugs or biologics and unapproved new animal drugs, however, cannot be exported except in the following two cases: 1) if the products are subject to an IND, providing the importing country's government has approved such imports; or 2) if the importing country's government formally requests through the U.S. Department of State that the product be exported (for purposes of clinical trials only) (21 C.F.R. j312.l(a)). As to unapproved animal biologics, there is some question about whether the VST Act applies to exports. Nevertheless, it is clear that FDA has authority over such exports, and, as indicated in the previously

● The FDA/USDA memorandum of understanding defines animal biologic products as those that "generally act through a specific immune process and are intended for use in the **treatment** (including prevention, diagnosis, or cure) of diseases in animals. Such products include but are not limited to vaccines, **bacterins**, sera, antisera, antitoxins, toxoids, allergens, diagnostic antigens prepared from, derived from, or prepared with **micro-organisms**, or growth products of microorganisms, animal tissues, animal fluids, or other substances of natural or synthetic origin. "

● 'h approved food additive can be exported if the exporter determines, without any need to inform or petition FDA, that the four conditions in sec. **801(d)(1)** of **FFDCA** are met. The same is true for a Class I medical device, but an unapproved Class II or Class III medical device cannot be exported unless a petition has been submitted to FDA and FDA has found that the exportation **is** not contrary to the public health and safety of the importing country and has the approval of the importing country, under sec. 801(d)(2) of **FFDCA**.

discussed memorandum of understanding, FDA could exercise that authority.

The U.S. policy of restricting the export of unapproved drugs and biologics is essentially based on paternalism. Many countries do not have the mechanisms either to evaluate or to regulate the quality of the drugs they import. In addition, there have been cases of drug dumping—situations where drugs deemed unsafe or ineffective by the United States or other developed countries have been marketed in less developed countries (25).

This policy has several implications for U.S. companies using biotechnology, and the implications may differ depending on the size of the company. In part because of the export restrictions, several of the large U.S. pharmaceutical companies have established manufacturing facilities in foreign countries, where their products are approved or where the law permits the export of unapproved products. These actions result in the transfer of technology, lost employment opportunities for U.S. workers, and lost opportunity to help the U.S. international balance of payments. These consequences can be expected to continue with respect to biotechnology products. The existence of such facilities in foreign countries may provide the large companies with at least a short-term competitive advantage over small, new biotechnology firms (NBFs). * The vast majority of the latter companies do not have and probably cannot afford to establish foreign facilities.

The export restrictions will also have an important implication for NBFs and for U.S. competitiveness in general because they may foster technology transfer to foreign companies with which they have joint ventures. In their joint ventures with large foreign companies, some NBFs in the United States are required to provide bulk product produced by the microorganism to the foreign partner, which would secure necessary approvals and purify, package, and market the drug in foreign markets. If the U.S. firm is unable to provide bulk product, the foreign partner then has the right to obtain the organism for its own use. The U.S. prohibitions on the export of unapproved drugs and biologics might be one reason why an NBF could not fulfill its agreement to supply bulk product to its foreign partner, thereby being required to transfer the organism and the technology.

In proposed revisions to the regulations governing the approval of new drugs, FDA has taken the position that bulk products, which it calls "drug substances," can be exported only if they are used in the manufacture of approved drugs and if certain labeling requirements are followed (30). FDA has proposed to define "drug substance" as "an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis . . . treatment or prevention of disease. . . ." (30). This definition would cover drug products produced by biotechnology, even if they required purification, packaging, and labeling, because such products usually will be active. At least one NBF in the United States has argued that section 801(d) of FFDCA should not be interpreted to prohibit the export of such substances for purposes of clinical trials (if the conditions of sec. 801(d) are met) and that such an interpretation will require it to transfer technology for the reasons mentioned in the preceding paragraph (9).

This entire problem concerning the export of unapproved drugs can be avoided in the future, however, without changes in the law or regulations. As mentioned previously, the current U.S. regulations allow the export of unapproved drug substances upon the formal request of the importing country's government. NBFs in the United States rightly point out that such requests are unlikely in cases where the government is actively seeking to encourage inward technology transfer. However, the NBFs' licensing agreements with foreign companies could be written so that the NBFs would not have to transfer the technology if the foreign company's government did not make the necessary request.

Imported Pharmaceuticals and Foreign Test Data.—Imported pharmaceuticals must meet FDA's IND and NDA requirements, even if approved for clinical testing or marketing in a foreign country. A question naturally arises regarding the acceptability of foreign test data.

● NBFs, as defined in ***Chapter 4: Firms Commercializing Biotechnology***, are firms that have started up specifically to capitalize on new biotechnology.

Currently, FDA will accept foreign clinical data in support of an NDA, but it very seldom approves an NDA solely on the basis of foreign data, even if the study that produced the data meets FDA requirements for well-conducted studies. Under proposed revisions to its regulations, FDA would consider approving NDAs based solely on foreign clinical trials on a case-by-case basis if: 1) the data are applicable to the U.S. population and U.S. medical practice; 2) the studies have been performed by investigators of recognized competence; and 3) FDA is able to assure itself of the validity of the data (30).

If adopted, the revised data requirements would have at least two implications for this country's competitiveness in biotechnology. First, they would allow large U.S. drug companies to continue their practice of conducting much of their clinical work in foreign countries where drug approval has been quicker than in the United States, but also to secure quicker drug approvals in the United States. Second, they would lessen a U.S. nontariff trade barrier faced by foreign firms.

U.S. DEPARTMENT OF AGRICULTURE

Under the VST Act, the manufacturer of an animal biologic to be sold interstate needs premarket clearance by getting licenses for the product and the factory from USDA. The agency has broad authority to require any data it thinks necessary to judge product identity, purity, safety, and efficacy. USDA regulation is generally seen as significantly less costly and time-consuming than FDA regulation. However, USDA's position on biotechnological products appears to be consistent with FDA's, i.e., such products will need a new license, even if identical to other licensed products, although data requirements may be lessened.

ENVIRONMENTAL PROTECTION AGENCY

EPA has extremely broad authority over chemicals, herbicides, and pesticides. Chemicals are covered by the Toxic Substance Control Act (TSCA) (15 U.S.C. §§2601-2629). TSCA is intended to fill gaps in other environmental laws. It authorizes EPA to acquire information on "chemical substances" in order to identify and evaluate potential hazards and then to regulate the production, use, distribution, and disposal of those substances. Commodity and specialty chemicals made by biotechnology (except those regulated under FFDCA) will face the same kind of regulation under TSCA as those chemicals made by conventional means. TSCA will also be applied to organisms used in the environment, as noted in the "Environmental Regulation" section below.

Pesticides, herbicides, and related products are covered by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (47 U.S.C. §§136(a)-(y)). FIFRA creates a premarketing clearance procedure under which EPA reviews data on safety and then registers the pesticide, provided it will not generally cause unreasonable adverse effects on the environment. EPA has proposed a rule on data requirements for such registration (36). Sections 158.65 and 158.165 of the proposed rule cover biological pest control agents, including genetically manipulated ones.*

European Economic Community countries

The Federal Republic of Germany, the United Kingdom, and France are members of the EEC, or Common Market, which was established by the Treaty of Rome in 1958.** The regulations of the EEC and the national regulatory processes of these three countries that are relevant to biotechnology products are discussed further below.

EUROPEAN ECONOMIC COMMUNITY

Since 1965, the EEC has issued a series of directives aimed at harmonizing the member states' testing and approval processes for proprietary medicinal products and veterinary medicinal products. None of these directives specifically deals with biotechnological products. The directives are important for the development of biotechnology because, to the extent biotechnological products are proprietary or veterinary medicinal products,*** their approval for manufacture or

*These sections set extensive data requirements on product performance, toxicology, residue analysis, hazards to nontarget organisms, and environmental fate and expression.

**The other members of the EEC are Belgium, Denmark, Greece, Ireland, Italy, Luxembourg, and the Netherlands.

***Proprietary medicinal products are drugs, biologics, or similar products sold under brand or trade names. In practice, most member states regulate biologics differently from chemically synthesized drugs and the European Community directives have not been used to try to harmonize those regulations.

marketing will be governed by national procedures conforming to the directives.

Although the ultimate aim of the EEC directives is to replace national drug approval processes with a Community-wide system, such a system is unlikely in the near future. The speed with which the EEC does achieve a Community-wide drug approval system, however, will have a significant impact on the development of biotechnology, because such a system could cut costs, provide uniform regulation, speed up the approval process, and open access to new markets.

Currently, the existing directives deal only with drugs and veterinary medicines, not biologics. The directives also deal only with some aspects of the pharmaceutical approval process—marketing authorizations and certain testing requirements. A system has been set up for obtaining multiple authorizations for marketing in EEC member states, but control over exports outside the EEC is entirely up to member states.

Council Directive 65/65/EEC established the basic regulatory framework with respect **to** drugs (4). It requires an authorization from the competent authority of a member state before a drug **can** be marketed in that state. It **sets** forth the required information that must be submitted to the authorizing agency and provides that authorization of the product shall be based on a finding of safety, efficacy, and quality. Licenses are to be granted for a 5-year period, subject to extension. A similar directive exists for veterinary medicine (5).

Two questions that will be important to biotechnology companies that manufacture drugs and that seek EEC marketing authorizations remain unanswered. The first concerns the so-called paper NDA issue. The EEC permits a new manufacturer of an already approved product to rely on published data to establish the safety, efficacy, and quality of its version. It is unclear, however, whether this policy will apply to biotechnological products. Under most member states' existing regulations, a change in manufacturing process from chemical to biotechnological synthesis requires either a new market authorization or an amendment to an existing one. Since the EEC has not addressed the issue, the individual member states will determine whether published tests results can be relied on or whether new tests must be undertaken.

A variation of this same issue involves unpublished test results. Under current regulatory policies for drug approvals in both Europe and the United States, the documents submitted in support of an application for approval of a drug (the "dossier") are treated as confidential. Proposals are being considered in Europe, particularly in the Federal Republic of Germany, to change the scope of the confidentiality of the dossier. one proposal is to retain the confidentiality of the dossier for a certain number of years, and then allow access to the information after the payment of compensation to the original manufacturer who performed the tests.

FEDERAL REPUBLIC OF GERMANY

The Law on the Reform of Drug Legislation of 1976 **sets** forth the approval process for drugs, biologics, and veterinary medicines (7). It is designed to conform with the relevant EEC directives, and responsibility for its administration lies with the Federal Health Office (BGA, Bundesgesundheitsamt).

The licensing procedure for new drugs and biologics produced through biotechnological processes will be the same as for more traditional products, A manufacturer of pharmaceuticals must obtain individual marketing authorizations to distribute each drug or biologic that it manufactures and separate manufacturing authorizations for each of its production plants. Generally, the drug approval process takes 4 to 6 months from the time the application is filed. In the case of biologics, BGA defers to the Paul Ehrlich Institute, which provides authorizations for the manufacture of sera, vaccines, test aUergens, test sera, and test antigens. Before deciding to approve a new drug or biologic, BGA must consult an independent commission of experts composed of physicians and representatives of the pharmaceutical industry. After an authorization for a drug or a biologic is given, BGA continues to monitor the competence of the managers and the adequacy of the facilities. An authorization may be withdrawn, revoked, or suspended if satisfactory standards are not maintained.

BGA regulations governing clinical testing of drugs and veterinary medicines track the applicable EEC directives. No specific prior approval of clinical testing is required, but BGA guidelines for such trials must be followed. The process for obtaining marketing approval and the information required in the application follows the EEC directives on proprietary medicinal products and on veterinary medicinal products. * In addition, the manufacturer must show that it holds a manufacturing license.

Anyone seeking to market an imported product must show that the product's foreign manufacturer has the equivalent of a manufacturing license and a marketing license in the country of manufacture; otherwise an explanation of why such authorization has not been granted must be supplied.

With respect to exports, it appears that a manufacturer intending to produce an item solely for export must comply with the requirements anci obtain a manufacturing license but need not obtain a marketing license.

Certain biologics, specifically sera, vaccines, or test allergens, may only be marketed if each batch is approved by the Paul Ehrlich Institute. Approval is given only if a test shows that the batch possesses the required safety, efficacy, and quality, and has been manufactured and tested by methods which conform to the standard set by scientific knowledge currently prevailing.

Several aspects of the Federal Republic of Germany's pharmaceutical approval process are of particular significance to pharmaceuticals produced by biotechnology, because a change in manufacturing process from chemical synthesis to biotechnology would necessitate a reauthorization of these products. In certain cases, a manufacturer must apply for reauthorization of a drug despite an existing authorization. The circumstances in which such a reauthorization must be sought include a change in the composition of the active constituents either in type or quantity, a change in dosage form, or an extension in the field of application. For biologics such as sera, vaccines, and test allergens, a change in the manufacturing process also requires a reauthorization.

Two regulatory issues currently being debated in the Federal Republic of Germany are also relevant. The first is a regulation now in force that requires any person who markets a drug in the country to maintain a legal presence in the Federal Republic of Germany. The EEC has recently ruled that this requirement is illegal and has asked that it be abolished, Whether the Federal Republic of Germany will do so remains to be seen.

The second issue involves current proposals to modify the confidentiality of drug authorization dossiers. As in most of Europe, no manufacturer in West Germany has access to confidential information in another manufacturer's dossier unless it specifically receives permission from the original manufacturer, permission which is usually granted, if at all, only after the payment of substantial compensation. A second manufacturer of a drug that has already been approved may also rely on published material in lieu of relying on the dossier or conducting its own tests, but most important drugs are not the subject of published studies. Almost any scientifically reliable material will be contained in the confidential dossier that the first manufacturer submitted. Under active consideration are proposals that would maintain absolute confidentiality of the dossier for a given number of years, but then allow for access to the dossier with a statutorily prescribed compensation system. It will probably be some time before any such system is enacted (8).

UNITED KINGDOM

Because the United Kingdom is a member state of the EEC, its regulations conform to the basic requirements of the EEC pharmaceutical directives. Its current standards are embodied in the Medicines Act of 1968 and in the regulations adopted under this statute. No specific regulations governing the approval of biotechnologically pro-

● The application data must contain data showing: 1) the toxicological effects and pharmacological properties of the drug; 2) its effectiveness in the given indications; *3)* the propriety of the suggested dosage; 4) side effects; 5) the drug is of appropriate quality'; and 6) the production control methods correspond to scientific knowledge currently prevailing and are suitable for quality assessment, An application for an authorization for veterinary medicines and medicated foodstuffs must include residue tests and indicate how long it takes for residues to occur in edible tissues and how such residues are to be assessed,

duced pharmaceuticals have yet been adopted, so such products are subject to the general approval process set forth in the Medicines Act. The approval process for pharmaceuticals and related substances is similar to the U.S. system in several respects, but it is somewhat less restrictive and much more efficient in terms of the time for approval.

The Medicines Act of 1968 provides a comprehensive framework for the regulation of "medicinal products" which include drugs, biologics, and veterinary medicines. Its provisions are administered by the Health and the Agriculture Ministers of the United Kingdom, acting with the advice of the Medicines Commission. The day-today operation of the act is the responsibility of the Medicines Division of the Department of Health and Social Security.

The regulations governing the use of medicinal products focus on the safety, efficacy, and quality of the product. The system utilizes five types of licenses: licenses as of right, clinical trial certificates, * product licenses, manufacturers' licenses, and wholesale dealer licenses. These licenses apply to the manufacture, sale, storage, import, or export of any medicinal product. The requirements for the issuance of clinical trial certificates are considered to be among the strictest in Europe. Before a certificate can be granted, an applicant must present animal pharmacokinetic data, acute and chronic toxicity data, and information on potential reproductive toxicity. The basic documentation required to obtain a product license is similar to that required by the relevant EEC directives. Trial certificates valid for up to 2 years and product licenses valid for 5 years are issued for drugs on which clinical testing and production began after September 4, 1971. Either may be renewed.

Additional requirements are imposed with respect to "biological," which include vaccines, toxins, antigens, sera, and enzymes. Such biological medicines are licensed on a batch release system. The manufacturing license requires that each batch of product be subject to certain tests and that samples and the results of the tests be submitted to the National Institute of Biological Standards and Controls (NIBSC). The basic tests administered by NIBSC, which may have to be modified in the case of new biotechnological applications, include potency, purity, toxicity, pyrogenicity, and immunogenicity.

NIBSC has begun considering how its testing requirements may have to be modified for biotechnological products but has not formally adopted new requirements (2). Among the issues which NIBSC has identified as requiring modification of its procedures for biotechnologically produced products are establishment of the identity of large proteins produced by rDNA technology, adaptation of bioassay techniques, biological potency, contamination of biotechnologically produced products with macromolecules of bacterial origin, and chemical modification of the required products.

Several aspects of the pharmaceutical approval process in the United Kingdom will be particularly relevant to the development of biotechnology. The batch release system for testing biologics will apply to many biotechnologically produced products, but that will be the case in many countries. Also of importance for biotechnology is the treatment of already licensed drugs produced with new methodologies. In the United Kingdom, such drugs require product and manufacturing licenses. However, the full documentation that would be required for a completely new drug need not be provided. The precise amount of documentation will vary with the particular drug. In general, the United Kingdom will allow the substitution of published references for actual test results in those situations permitted under the EEC Council Directive 65/65/EEC (4). However, a second manufacturer is not permitted to rely on the confidential information submitted in the dossier of a first manufacturer. Thus, a new manufacturer of an already approved drug is required independently to demonstrate the safety, efficacy, and quality of the drug through its own research or that of independent researchers.

Imported drugs also require a product license. The manufacturer may be required to declare that any requirements imposed by the law of the country in which the drugs are manufactured

"Licenses of right and clinical trial certificates are self-limiting. The trial certificates terminate automatically once the trial process has ended. Licenses of right are transformed into product licenses once the drug has been reviewed by the Medicines Review Commission and found safe, effective, and of proper quality.

have been complied with and to permit the licensing authority to inspect his premises to ensure that they comply with any prescribed conditions of the license. Drugs produced solely for export also must be licensed, but the licensing authority is required to consider only quality, not the safety and efficacy of the drug.

FRANCE

The French approval processes for pharmaceuticals includes many of the same steps as the processes in the United States. The basic standards for approval are quality, safety, and efficacy of the pharmaceuticals, and the necessary tests are largely the same.

The authority responsible for the registration of new drug products is the Directorate of Pharmacy and Medicaments of the Ministry of Health, which administers the requirements of the Public Health Code, Book V, and the EEC protocols for analytical, toxicological, and pharmacological tests and clinical trials. The Ministry of Health uses the same basic standards of quality, safety, and efficacy required by the EEC.

A manufacturer must notify the Ministry of Health before commencement of clinical trials of a new product or for a new indication of an established product. The trials must be carried out under the supervision of an "approved expert"* and must follow procedures and present data in the format established by the Ministry of Health. Toxicological and pharmacological data must be submitted to the approved expert prior to commencement of the trials. Except for the analytical data, the information does not have to be generated by local French studies; however, the foreign data can only be accepted if it is justified by approved experts and conforms to EEC protocols. These rules apply also to clinical data generated by studies conducted abroad. Clinical trials must be performed in hospitals as controlled experiments.

Prior to obtaining a marketing license, a manufacturer is also required to request authorization from the Directorate of Pharmacy and Medicaments to manufacture the new drug product. If the product is to be manufactured abroad, the manufacturer must attach to the French marketing application the document granting it authority to manufacture the product in the foreign country. The marketing authorization itself is subject to the documentary requirements established by the EEC directives.

Once a manufacturer has submitted all relevant data to the Ministry of Health, the Minister must announce a decision on the application for marketing registration within 120 days. This period may be extended for another 90 days in exceptional cases. In practice, however, the processing time for an application averages 6 to 8 months. A second manufacturer cannot rely on the dossier of a first manufacturer to qualify its drug, so a new manufacturer making an already approved drug by biotechnological processes would have to show the drug's safety, efficacy, and quality all over again. However, as in other EEC countries, a manufacturer may rely on some published data to support its application.

Once registration has been approved, as in the rest of the EEC, the marketing license is valid for 5 years. It may be renewed for additional 5-year periods only if the manufacturer formally declares that no modification has occurred in the scientific data submitted in support of the original application. The Ministry of Health must therefore be notified of any new data.

A drug may be imported from another EEC country and, in exceptional circumstances, from a non-EEC country, provided that a marketing license has been obtained in France. A certificate is required proving authorization for sale or distribution within the exporting country. Authorization for the marketing of an imported drug is only valid for 6 months, but presumably may be renewed.

Drug products designed for animal consumption are also regulated by the Ministry of Health. The application procedures for obtaining authorization to market veterinary drugs are basically the same as those for human drugs.

* **"Approwd experts" are scientists with expertise in various aspects of pharmaceutical testing who are approved by the Minister of Health.** The Minister maintains lists of these experts from among whom an applicant may select experts to review his or her data and supervise further testing. Approved experts need not be French.

Switzerland

The Intercantonal Convention for the Control of Medicaments is the authority for the regulation of drugs and related products. Under the Convention, the Intercantonal Office for the Control of Medicaments (IOCM, Interkantonale Kontrollstelle fti Heilmittel) administers the drug regulatory system. IOCM has four principal tasks: quality control of marketed drugs, quality control of manufacturing, the licensing of new drugs, and the review and relicensing of existing drugs. IOCM has responsibility for pharmaceuticals, * veterinary medicines, and medical devices. Food and cosmetics are controlled by the Federal Office of Public Health under separate Federal authority. The quality control functions of IOCM are exercised through sampling of drugs at the time of their registration and periodically thereafter and through periodic inspections of pharmaceutical facilities.

The licensing of pharmaceuticals is much more streamlined than in other countries. There is no requirement for government approval before initiation of clinical trials. This is due both to the small size of IOCM and to greater reliance on the good faith of manufacturers and the common sense of medical practitioners participating in the clinical trials of new drugs.

Approval of the marketing of a drug is based on its efficacy and safety, which are judged by an independent board of university scientists. Approval can be refused not only if the drug is found not to be safe and effective, but also if its price is excessive. Licenses are issued for a 5-year period and may be renewed by the same board.** The drug approval process generally takes 6 to 10 months.

Of particular importance for biotechnology is the fact that less documentation is required for drugs that are not new chemical entities. Switzerland's streamlined drug approval process should mean faster action on new drug applications and on old drugs being produced through biotechnology.

For imports, it is necessary to have a certification that the drug is authorized for sale or distribution in the country of manufacture and that the manufacturer is subject to regular inspection. Drugs intended solely for export are exempt from registration, but voluntary registration can be made.

Japan

The approval process for drugs, biologics, and veterinary medicines in Japan is set forth in the Pharmaceutical Affairs Law (17). The law generally requires each manufacturer or importer to obtain a license for each manufacturing plant or business office and a separate approval for each drug manufactured or imported. * The manufacturer's or importer's license must be renewed every 3 years. The product approval has no set duration, but in practice many drugs are reviewed again after 6 years. The approval process is quite drawn out and complex because many agencies are involved. The time from submission of an application to approval is supposed to take 1 to 3 years but in practice takes longer (13).

The information that must be filed with the application for the approval of a new drug in Japan include data on origin, discovery, use in foreign countries, physical and chemical structure and properties, stability, various forms of toxicity and other dangerous side effects, pharmacological action, how the drug will be used in the body, and results of clinical trials **(15). Most of** the **data** is required to be published as an original article in a Japanese scientific journal. Data on animal tests for toxicity must meet certain special requirements. The application will be denied if the drug has no effect, efficacy, or efficiency as indicated in the application, if the drug is "remarkably dangerous" in comparison to its effect, or if the drug has been designated improper under the Ministry of Health and Welfare Ordinance **(17).**

An application to import a new drug must meet these standards. It must also contain a document

"This includes in vivo diagnostics, contraceptives, narcotics, anesthetics, antibiotics, some industrially produced **homeopathic** medicines, herbal remedies, **radiopharmaceuticals**, and certain blood products.

" "In special cases, **up-to-date** analytical, **preclinical**, and chemical data as well as samples may be required if requested by 10CM,

*The separate approval for each drug is unnecessary if the drug is listed in the Japanese Pharmacopoeia and has been exempted by the Minister for Health and Welfare.

certifying that the exporting country approves its manufacture and copies of the import contract or similar document (16). The import or manufacture of biologics is prohibited unless special requirements concerning their processing, properties, quality, and storage are met (16). Each batch of biologics must be tested and approved by the National Institute of Health.

New drugs must be reexamined about 4 to 6 years after approval, largely so that the safety of the drug can be assessed in light of post-approval clinical tests and other scientific research. The reexamination is to determine whether the drug now displays any condition that would, if a new drug application were now filed, require its rejection, i.e., that the drug is not efficacious, is more dangerous than efficacious, or has been designated improper (17). The approval for a drug may be canceled if the drug cannot pass reexamination, if health or sanitation reasons so require, if the licensee fails to submit accurate reexamination material, or if the licensee has not produced the drug for 3 years (17). How this will affect drugs produced with biotechnology is unclear.

Environmental regulation *

Protection of the environment is one aim of the rDNA guidelines in each of the competitor countries; none of them have any other rules specifically directed to the environmental effects of biotechnology. Nevertheless, the more general environmental laws will apply to biotechnological processes, products, and waste products. The extent to which these general laws will apply to genetically modified organisms used in the environment is uncertain in all of the countries except the United States, where EPA has asserted jurisdiction under TSCA.

The environmental requirements in the rDNA guidelines are likely to have little effect on the competitive position of any country. The specific measures required for any physical containment level vary little from country to country, Moreover, most rDNA activities are now conducted at low containment levels that require essentially only that good microbiological practices be followed. Deliberate release of genetically modified organisms is generally prohibited, although procedures exist for exceptions from the prohibition. In the United States, deliberate release is not prohibited as such, but one who would do so under the guidelines must have the approval of IBC and NIH, after consultation with the Recombinant DNA Advisory Committee. *

It is difficult to determine what effect, if any, the more general environmental regulations of each country dealing with air and water pollution and waste disposal will have on biotechnology in that country. Since much of the environmental regulation in any country is performed on the local level, generalizations about national environmental controls can be misleading. States (Lander) in the Federal Republic of Germany, for example, are about to enact specific legislation to fill in the framework set up by Federal laws. Certain environmental legislation in Japan, though enacted at the national level, applies only to certain areas. Local authorities in France and the United Kingdom possess considerable responsibility for administering and enforcing environmental rules. Switzerland leaves most decisions on environmental regulation to the cantons, as it does decisions on other subjects. The United States has one of the more centralized systems for environmental control, but even Federal statutes allow for responsibility to be transferred to the States.

*For specific information regarding the six countries, see the section on environmental regulation in *Appendix F: Recombinant DNA Research Guidelines, Environmental Laws, and Regulation of Worker Health and Safety*.

*A lawsuit has heen filed against NIH claiming that approval by the Recombinant DNA Advisory Committee is not consistent with the National Environmental Policy Act and claiming that an Environmental Impact Statement must be prepared (*Foundation on Economic Trends v. Heckler*, 56 U.S.L.W. 2714 (D.D.C. Sept. 14, 1983)).

All of the countries except Switzerland have fairly comprehensive and stringent environmental regulation. Switzerland's national regulation is directed only toward water pollution. Thus, its biotechnology companies may have a competitive advantage over those in the other countries because of less restrictive environmental regulation. Yet even the more stringent regulation in other countries would not necessarily handicap companies because the regulation is directed mainly toward toxic chemicals. The degree of traditional environmental problems that companies using biotechnology might create—air and water pollution and hazardous waste-does not now appear to be so great that environmental controls will significantly affect the commercialization of biotechnology. However, increasing commercialization of biotechnology eventually will require more consideration about the disposal of waste byproducts. All countries are now about equal in this area, but those who undertake to resolve uncertainties about the specifics of that regulation should enhance the competitive positions of their biotechnology companies.

The United States seems to be the farthest ahead in considering the risks and regulation of the deliberate release of genetically modified organisms. This may simply be the result of the fact that this area of biotechnology is further along in the United States than in the other countries. In any event, NIH recently has reviewed and approved several proposals to release organisms into the environment. Also, on June 22, 1983, two congressional subcommittees held a joint hearing on the topic of regulating such releases (22).

At the hearing, EPA took the position that such organisms are "chemical substances" as defined by TSCA * and therefore subject to regulation by EPA under TSCA (3). Although the matter is not free from doubt, a consensus has been developing among the experts that TSCA would apply (18).

TSCA gives EPA broad authority to regulate the products of biotechnology, and, assuming EPA's interpretation of the definition of "chemical substance" survives any subsequent legal challenge, TSCA would have great potential for regulating the deliberate release of genetically modified organisms. Under section 4 of TSCA, EPA can adopt rules requiring testing of chemical substances that "may present an unreasonable risk of injury to health or the environment" or will be produced in substantial quantities (and enter the environment in substantial quantities or result in substantial human exposure) when existing data are insufficient to make a determination and testing is necessary to develop adequate data. Section 5 requires the manufacturer of a new chemical substance to notify EPA 90 days before beginning production and submit any test data it may have on the chemical's health or environmental effects. If the agency decides that the data are insufficient for evaluating the chemical's effects and that it "may present an unreasonable risk of injury to health or the environment" or will be produced in substantial quantities (and enter the environment in substantial quantities or result in substantial human exposure), it can propose an order to restrict or prohibit the chemical substance's manufacture or use. Under section 6, EPA can prohibit or regulate the manufacture or use of any chemical substance that "presents, or will present an unreasonable risk of injury to health or the environment. " TSCA also provides for recordkeeping and information gathering about the environmental and health effects of chemical substances.

Despite its theoretical applicability, TCSA may leave much to be desired in terms of a practical program to regulate the use of genetically manipulated organisms in the environment. First, EPA has little expertise or experience in the area of genetic manipulation. Second, its toxic substances program has been significantly understaffed, according to a 1980 study by the U.S. General Accounting Office study (21), Third, TSCA may not give EPA sufficient regulatory power, if the risks presented by deliberate release are viewed as substantial, For example, section 5, which creates the premanufacturing notice requirement, does not require the generation of toxicological data. A recent OTA background paper found that nearly half of the premanufacturing notices submitted

* A '{chemical substance" is defined in the relevant part under sec. 3(2)(A) of TSCA as "any organic or inorganic substance of a particular molecular identity," including "any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature. . . ."

to EPA do not have information about the chemical's toxicity (26). * Moreover, the burden is on EPA to take legal action if it believes that insufficient data exists for a new chemical substance.

USDA also has an environmental role to play with respect to biotechnology. It regulates importation and interstate shipment of plants, animals, and their pathogens (21 U.S.C. \$lO1-135; 7 U.S.C. \151-167; 7 U.S.C. \150aa et seq.). Thus, some of the "raw materials" of interest to biotechnologists in the agriculture field are subject to USDA restrictions. For example, two potential mechanisms for transferring genes into plants are the bacterium ***Agrobaclerimn Imnefaciens*** with its integrating Ti plasmid and the cauliflower mosaic virus. Both the bacterium and the virus are subject to the restrictions. Similarly, work with particularly dangerous animal viruses may be prohibited or severely restricted. For example, work on foot and mouth disease virus can only be performed at Plum Island, a high containment USDA laboratory located off the coast of Long Island, N.Y. USDA also bars entry into the United States of 22 other pathogens that might be of interest to companies desiring to produce animal vaccines.

● As to the importance of such information, OTA's background paper stated (26): "Certainly, the absence of toxicity data complicates EPA's efforts to decide whether a new chemical may present an unreasonable risk to health or the environment. But the importance of toxicity data for making decisions about particular chemicals varies. Those data are less important for chemicals that closely resemble others for which there is much information and experience. They are critical for unusual chemicals or chemicals for which there is limited information. "

Regulation of worker health and safety*

The rDNA research guidelines in each of the six countries (but not those of the EEC itself) contain provisions for the safety and health of laboratory workers. Each country also has more widely applicable laws and regulations, but it is the rDNA guidelines that will have the most immediate impact on the biotechnology companies.

The substance of the various worker health and safety provisions in the national rDNA guidelines varies among the six countries studied, although most set forth rules to ensure that laboratory workers are knowledgeable about laboratory procedures, that emergency procedures are known and safety equipment is available, and that worker health is monitored for certain types of work. It seems fair to infer that the costs and burdens associated with these requirements are modest, because there has been little criticism or complaints about them from academia or industry (8).

The more general worker health and safety laws in the United States and in each of the five foreign countries have had no measurable effect as yet on the industries using biotechnology in each country. Each country imposes general duties on employers to maintain safe workplaces and to eliminate or control hazardous substances (although when these substances are specified, they do not include materials likely to be found in a biotechnology laboratory). The most that can be said is that each country has at least one authority able to impose further requirements to protect worker health and safety, but none has yet done so. Such requirements would be primarily process rather than product oriented.

The United States has studied the question of the possible risks posed to workers from long-term exposure to novel organisms and products. The Centers for Disease Control and the National Institute of Occupational Safety and Health (NIOSI-1) created an ad hoc working group on medical surveillance for industrial applications of rDNA. The group concluded that, while physical containment of rDNA-containing organisms and their products is the first line of defense, medical surveillance of industrial workers can play a valuable auxiliary role in protecting their health (19). Others have disagreed with this finding, questioning the need for surveillance and the ability to construct a meaningful program.

● For specific information regarding the six countries, see section on regulation of worker health and safety in *Appendix F: Recombinent DNA Research Guidelines, Environmental Laws, and Regulation of Worker Health and Safety*.

The NIOSH findings have not been implemented by the Occupational Safety and Health Administration (OSHA), the U.S. agency primarily responsible for worker safety and health. Under the Occupational Safety and Health Act of 1970, OSHA can promulgate workplace standards to protect workers from toxic substances or harmful physical agents. Under a recent decision by the US. Supreme Court (12), such standards must be "reasonably necessary to remedy a significant risk of material health impairment. " Although this requirement would appear to prevent OSHA from acting on those purely conjectural risks associated with biotechnology, the agency could act on known biological risks (e.g., those presented by known pathogens), or physical risks (e.g., those presented by the use pressurized containment vessels). In any event, OSHA has not promulgated any standards for bioprocesses in general, nor has it taken any position on regulating biotechnology.

At this point and for the foreseeable future, worker health and safety regulation of biotechnology is minimal. Thus, it will give neither an advantage nor a disadvantage to any of the competitor countries.

Findings

Health, safety, and environmental regulation can affect the cost, time, and financial risks of getting products to market. Thus, such regulation can be expected to affect international competitiveness in biotechnology.

The only government controls directed specifically toward biotechnology are the rDNA guidelines adopted by the EEC and the six competitor countries. They are essentially voluntary and directed primarily at research, although they do apply to large-scale work to varying degrees. Their containment and oversight provisions have been substantially relaxed since they were originally adopted, and this trend is expected to continue.

The rDNA guidelines in the competitor countries are quite similar in their regulatory goals, requirements, and implementation because they are generally patterned after the U.S. guidelines, which were initially developed through the efforts of the international scientific community. Nevertheless, there are differences that allow the guidelines to be ranked in terms of their restrictiveness and potential impact on the competitiveness of the various countries.

The rDNA guidelines of the United States are the least restrictive of the guidelines in any of the competitor countries. The vast majority of the experiments that are done with the most commonly used host-vector systems are either exempt or can be done at the lowest containment levels. Prior approval, even by the IBCs, is required only for a limited category of experiments. The rDNA research guidelines of Japan and the European countries are more restrictive than the U.S. guidelines in one or more of the following ways:

- they require more stringent containment;
- they require more time-consuming approval procedures;
- they have fewer categories of approved host-vector systems; or
- they severely restrict large-scale work.

Japan has the most restrictive rDNA guidelines. A limited number of host-vector systems have been approved for use. More importantly, companies have had extreme difficulty in obtaining approval to do work with more than 20 liters of culture, but this is expected to change soon.

Of the remaining countries, Switzerland appears to have the least restrictive guidelines. Its Government has played no role in the guidelines, and there are no requirements covering large-scale work. However, Switzerland follows an earlier, and thus more restrictive, version of the U.S. guidelines. The guidelines in France and the United Kingdom appear to be roughly equivalent with regard to their impact on biotechnology. The Federal Republic of Germany appears to be slightly more restrictive, primarily because Government approval must be obtained before even moderate risk experiments can be started.

It is the existing regulation that will most affect biotechnology: product approval laws, environmental laws, and worker health and safety laws. The most important of these for biotechnology will be the product approval requirements, especially for pharmaceuticals and veterinary medicines because those products are the most stringentl$_y$ regulated or the subject of much of the current effort in product development. For this reason, and because of insufficient information on foreign regulation of the other products, the analysis for product approval in this chapter concentrated on the regulation of pharmaceuticals and veterinary medicines,

With respect to the product approval process, particularly for pharmaceuticals and animal drugs, the United States appears to be at a competitive disadvantage with respect to all of the other countries except Japan. The competitive disadvantage for the United States results mainly from the time and cost necessary to secure premarketing approval. In contrast, the United Kingdom has the most expedited pharmaceutical approval process, even though its substantive requirements are quite similar to those of the United States. Switzerland is the least restrictive of the countries in terms of substantive requirements. For example, it does not require Government approval before initiation of clinical trials, In contrast to pharmaceuticals and animal drugs, the regulatory requirements for animal biologics are less restrictive in the United States and roughly on par with those in other countries.

Another reason the United States is at a competitive disadvantage is that the United States, in contrast with the other countries, does not allow the export of unapproved pharmaceuticals. In addition, bulk drug products may also not be able to be exported, Given certain provisions in joint venture agreements between U.S. NBFs and their foreign partners, these requirements could enhance the transfer of biotechnology to foreign companies.

Specific requirements regarding biotechnology products are or will be set at the agency level within the existing statutory framework. In the United States, FDA has taken the lead in developing and publishing informal statements. Since these statements help dispel uncertainties, they will help product development. In its policy statements, however, FDA has taken the position that rDINA products whose active ingredients are identical to ones already approved or to natural substances will still need to go through the new product approval process. However, data requirements may be modified and abbreviated. This appears not to be the situation in other countries, although there have not been definitive pronouncements by the regulatory agencies.

one area of uncertainty that could hinder U.S. competitiveness in biotechnology to some degree is the question of jurisdiction over animal biologics. FDA and USDA are engaged in a jurisdictional dispute that could delay product approvals.

Environmental and occupational safety and health regulations are not likely to give any of the countries a significant competitive advantage in biotechnology. This regulation is likely to play a minor role, except in the area of deliberate release of genetically manipulated organisms into the environment. For that application of biotechnology, uncertainties exist as to what, if any, kind of special regulation will develop. The United States appears to be the farthest along in considering the problem; thus, to the extent that decisions are made and the regulatory picture clarified for corporate planners, the United States may have a slight advantage.

Issue and options

ISSUE: How could Congress improve U.S. competitiveness in biotechnology through changes in the regulatory environment?

Regulation imposes costs, constraints, and delays on biotechnology companies that are justified when they promote such general goals as the enhancement of human health or quality of the environment. To the extent that such regulation is inefficient or unnecessarily restrictive or creates uncertainties that impede business planning, however, it will restrict biotechnological innovation and U.S. competitiveness in biotechnology without achieving the other goals.

OTA has identified several options that could improve U.S. competitiveness in biotechnology through changes in laws, regulations, and administrative policies regarding health and safety. Many of these are not specific or limited to biotechnology but nevertheless could significantly affect this technology. Furthermore, many of the actions could be taken by executive agencies, and, in fact, are being considered. Nevertheless, Congress may decide legislative action is necessary or more appropriate.

Option 1: Amend the Federal Food, Drug, and Cosmetic Act (FFDCA) to permit the export of unapproved drugs and biologics.

of the six competitor countries identified in this assessment, the United States is the most restrictive regarding the export of unapproved drugs and biologics. The relevant provision of FFDCA is designed to prevent "drug dumping' '—situations where drugs deemed unsafe or ineffective by the United States or other developed countries have been marketed in developing countries.

Those who advocate eliminating this provision of FFDCA argue that a US. company can have ethical reasons for wanting to export a drug that is unapproved by FDA. For example, it may be supplying a company that sells the drug in a country that has approved the drug for sale. Advocates of eliminating this provision also argue that the provision simply embodies U.S. paternalism toward other countries, which are capable of making their own health and safety decisions. Partly to avoid the U.S. ban on the export of unapproved drugs, the multinational drug companies have established foreign manufacturing facilities. This practice results in the transfer of technology and jobs from the United States and has an adverse effect on the U.S. balance of payments. For NBFs, which may not have the money to establish foreign facilities or the time before contract revenues and capital run out, the export restriction may be especially burdensome.

FDA has taken the position that bulk pharmaceutical products made by biotechnology are drugs because such products are biologically active; thus, the export prohibition of FFIICA applies. One U.S. company, Genentech, has asserted that its inability to sell bulk pharmaceutical products to its foreign joint venturers will result in its being required to transfer the technology to produce that bulk product to its foreign partners. This company has argued that bulk pharmaceutical products produced by biotechnology and not labeled as drugs should not be considered drugs under FFDCA and FDA regulations. Clearly, this question of interpretation could be resolved on the administrative level without congressional action. To change the general prohibition in FFDCA against the export of unapproved human and animal drugs and biologics, however, legislation would be necessary.

The arguments against amending FFDCA to permit the export of unapproved drugs and biologics are essentially moral ones. There have been documented cases of drug dumping in developing countries. Supporters of the existing restrictions argue that the United States has a moral duty to try to prevent such actions and that the developing countries are unofficially in favor of these export restrictions.

There are several different ways that legislation to permit the export of unapproved human and animal drugs and biologics could address these moral arguments. First, the legislation could exclude products that have actually been barred by FDA. Second, it could permit the export of unapproved drugs and biologics only if they have

been approved by at least one other developed country. Third, it could permit the export of unapproved drugs and biologics only to countries where the products has been approved. Finally, the legislation could be drafted so that unapproved drugs and biologics can be exported only to developed countries. The potential diplomatic problems that could arise by having to decide which countries are "developed" could be avoided or lessened by using the definitions of various international organizations, such as the International Monetary Fund.

Option 2: Pass legislation to merge the Virus, Serum, Toxin Act of 1913 into the Federal Food, Drug, and Cosmetic Act.

The reasons for the different statutes are primarily historical, and the distinctions between animal drugs and biologics, if they were not already anachronistic, have virtually been made so by rDNA and hybridoma technology. Nevertheless, USDA and FDA were engaged in a jurisdictional dispute over bovine interferon and may well continue to engage in disputes over future products. By trying to satisfy both agencies, U.S. companies using biotechnology are likely to incur additional costs and delays. In addition, the uncertainties over regulatory authority may hinder corporate planning for what product areas to pursue or may steer firms away from pursuing these kinds of products. As a result, U.S. firms may be at a competitive disadvantage with respect to foreign firms.

Although combining the regulatory jurisdiction into one agency, FDA, may make sense conceptually, there will be substantial institutional barriers to doing so. If USDA is unwilling to give up its jurisdiction, as it appears to be, it can count on substantial political support from inside and outside of government. In addition, despite the adverse consequences of this jurisdictional dispute, the biotechnology companies themselves may well prefer USDA to retain or enhance its jurisdiction over animal biologics because USDA regulation is viewed as substantially less burdensome and costly than FDA regulation. This option has been proposed several times in past years, but there has been little progress toward its implementation.

Option 3: Amend the patent law to extend the term of patents on products or processes that need regulatory approvals before marketing.

This option was considered extensively by the 97th Congress, in which legislation passed the Senate and failed to pass the House by a few votes. It was also the subject of an OTA report, *Patent-Term Extension and the Pharmaceutical Industry* (24). Legislation to accomplish this option (S. 1306, H.R. 3502) has been introduced in the 98th Congress.

Firms that are heavily involved in basic research support patent-term extension. They claim that R&D costs and risks are rising, yet the effective life of patents on the products resulting from the R&D is declining because of the increasing time necessary for securing regulatory approvals before marketing. Since this may cause returns on R&D investments to decrease, the firms assert that innovation will suffer. Several biotechnology firms have supported this option publicly.

Generic drug producing firms and consumer groups oppose patent-term extension. The generic drug firms, which derive most of their revenues from drugs equivalent to the pioneering ones whose patents have expired, assert that patent-term extension will delay their entry into the market or not make that entry worthwhile because of limited product life remaining. They also assert that patented products often maintain an exclusive market position after their patents expire because of nonpatent barriers to market acceptance of generically equivalent products. As a result, patent-term extension would cause competition to decline and prices to increase. The consumer groups support this position and also note that the pharmaceutical industry has been extremely and consistently profitable for a great many years, even while the regulatory burdens have been increasing.

The OTA report mentioned above found that "[t]he evidence that is available neither supports nor refutes the position that innovation will increase significantly because of patent-term extension." It did note, however, that the incentives provided by patents for pharmaceutical R&D would be enhanced.

Option 4: Address the uncertainties and concerns about the deliberate release of genetical!y manipulated organisms into the environment by passing new legislation or amending the Toxic Substance Control Act to clari - [v its applicability to living organisms.

There are risks associated with releasing nonindigenous organisms into the environment. Although most nonindigenous such organisms do not establish an ecological niche, many have done so with disastrous consequences. For example, over half of the insect pests in the United States today came from abroad; similarly, the microorganism causing Chestnut blight was not indigenous to the United States.

The risks of releasing genetically manipulated organisms into the environment are not known. On one hand, changing the genetic makeup of an organism usually decreases its ability to survive. On the other hand, many of these organisms, such as microbes used for enhanced oil recovery, will have to be manipulated so as to be competitive with indigenous micro-organisms and to be able to withstand extreme environments in order to be able to accomplish the task. Some industry spokespeople, who believe that rDNA-containing microorganisms do not present any special risks when properly contained in bioreactors, have expressed concern about the deliberate release of such micro-organisms into the environment.

The concern about releasing genetically manipulated organisms into the environment and the uncertainties about the Federal Government's authority to regulate such activities may impede developments in the use of biotechnology in areas such as microbial enhanced oil recovery, pollution control, and mineral leaching. It may even hinder genetic manipulation of plants, * although the risks involved are seen as much less than those for micro-organisms. Given the concern about risk and the uncertainty over the Federal Government's possible regulatory response, U.S. companies may have difficulty planning where to place limited resources for research and product development.

Opponents of this option are likely to question whether legislative action is needed to accomplish the goal of environmental protection. Although most experts acknowledge that there is uncertainty about whether TSCA covers organisms, a consensus seems to be developing that it does. More importantly, EPA has taken the position that TSCA applies. In addition, voluntary oversight is being exercised by the Recombinant DNA Advisory Committee, although the quality of that oversight is the subject of litigation.

● **The U.S. Recombinant DNA Advisory Committee (RAC) recently approved a change in the guidelines that would permit field tests with plants containing rDNA with the prior approval of the local Institutional Biosafety Committee and a working group of the RAC** under certain conditions.

Chapter 15 references* —

1. Bozeman, N. H., "The Regulation of Hybridoma Products)" ***The Impact of Hybridoma Technology on the Medical Device and Diagnostic Product Industry,*** T. J. Henry (cd.) (Washington, D.C.: Health Industry Manufacturers Association, 1982).
2. Bristow, A. F., and Bangham, D. R., "The Control of Medicines Produced by Recombinant DNA Technology, " ***Trends in Biological Science*** (Amsterdam: Elsevier / North-Holland Biomedical Press, August 1981), 6: VI-VIII.
3. Clay, D. R., Acting Assistant Administrator, Office of Pesticides and Toxic Substances, Environmental Protection Agency, statement in ***Environmental Implications of Genetic Engineering,*** hearings before the Subcommittee on Science, Research, and Technology and the Subcommittee on Investigations and Oversight, House Committee on Science and Technology, U.S. Congress, June 22, 1983 (Washington, D.C.: U.S. Government Printing Office, 1983).
4. Council of the European Communities, Council Directive of 26 January 1965, No. 65/65/EEC, on the Approximation of Provisions Laid Down by

● **Note: F.2d = Federal** Reporter, **Second Series S Ct. = Supreme Court** Reporter.

Law, Regulation or Administrative Action Relating to Proprietary Medical Products, *Official Journal of the European Communities*, 22, Feb. 9, 1965, reprinted in Commission of the European Communities, *The Rule Governing Medicaments in the European Community*, Catalogue No. CB-24-78-120-EN-C (Brussels: Office for Official Publications of the European Communities, May 1978).
5. Council of the European Communities, Council Directive of 28 September 1981, No. 81/851/EEC, on the Approximation of the Laws of the Member States Relating to Veterinary Medicine Products, *Official Journal of the European Communities*, 24 (L317):1-15, Nov. 6, 1981.
6. Cunningham, B., General Counsel, Genentech, Inc., South San Francisco, Calif., personal communication, May 5, 1983.
7. Federal Republic of Germany, Arzneimittelgesetz (Law on the Reform of Drug Legislation) of 24 August 1976 Bundesgesetzblatt [BGB1] 2445 (W. Ger.), nonofficial translation edited by Federal Ministry for Youth, Family Affairs, and Health, Bonn, 1977.
8. Fox, A., and Sciortino, J. (of Kaye, Scholer, Fierman, Hays, & Handler), "International Health and Safety Regulation of Biotechnology," contract report prepared for the Office of Technology Assessment, U.S. Congress, July 1983.
9. Genentech, Inc., "Supplemental Comments by Genentech, Inc. on Proposed New Drug and Antibiotic Regulations," U.S. Food and Drug Administration Docket No. 82N-0293 (Jan. 5, 1983). [comments on file at FDA]
10. *Grand Laboratories, Inc.* v. *Patricia Harris*, 660 F.2d 1288 (8th Cir. 1981).
11. Hayes, A. H., Jr., Commissioner, Food and Drug Administration, statement in *Patent Term Extension and Pharmaceutical Innovation,* hearings before the Subcommittee on Investigations and Oversight, House Committee on Science and Technology, U.S. Congress, Feb. 4, 1982 (Washington, D.C.: U.S. Government Printing Office, 1982).
12. *Industrial Union Department, AFL-CIO* v. *American Petroleum Institute,* 100 S. Ct. 2844 (1980).
13. International Federation of Pharmaceutical Manufacturers Association, *Legal and Practical Requirements for the Registration of Drugs (Medicinal Products) for Human Use,* 2d ed., 1980.
14. *Japan Economic Journal*, "Council Helps Biotech Firms by Easing 20-liter Regulation," 21:16, June 21, 1983.
15. Japan, Enforcement Regulations, Article, 18-3; *Requirements for the Registration of Drugs in Japan* (Yakuji Nippo, Ltd., 1982).
16. Japan, Ministry of Health and Welfare, Pharmaceutical Affairs Bureau, *Pharmaceutical Administration in Japan*, 2d ed., Tokyo, Japan, February 1980.
17. Japan, Pharmaceutical Affairs Law, Law No. 145 of August 1960.
18. Karny, G. M., Senior Analyst, Biological Applications Program, Office of Technology Assessment, statement in *Environmental Implications of Genetic Engineering,* hearings before Subcommittee on Science, Research, and Technology and the Subcommittee on Investigations and Oversight, House Committee on Science and Technology, U.S. Congress, June 22, 1983 (Washington, D.C.: U.S. Government Printing Office, 1983).
19. Landrigan, P., Cohen, M., and Dowdle, W., "Medical Surveillance of Biotechnology Workers: Report of the CDC/NIOSH Ad Hoc Working Group on Medical Surveillance for Industrial Applications of Biotechnology," *Recombinant DNA Technical Bulletin* 5(3):133-138, 1982.
20. U.S. Congress, General Accounting Office, *FDA Drug Approval—A Lengthy Process That Delays the Availability of Important New Drugs*, Washington, D.C., 1980.
21. U.S. Congress, General Accounting Office, *Report to the Congress: EPA Is Slow To Carry Out Its Responsibility To Control Harmful Chemicals*, Washington, D.C., Oct. 28, 1980.
22. U.S. Congress, House Committee on Science and Technology, *Environmental Implications of Genetic Engineering,* hearings before the Subcommittee on Science, Research and Technology and the Subcommittee on Investigations and Oversight, House Committee on Science and Technology, U.S. Congress, June 22, 1983 (Washington, D.C.: U.S. Government Printing Office, 1983).
23. U.S. Congress, Office of Technology Assessment, *Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals*, OTA-HR-132, Washington, D.C., April 1981.
24. U.S. Congress, Office of Technology Assessment, *Patent-Term Extension and the Pharmaceutical Industry,* OTA-CIT-143, Washington, D.C., August 1981.
25. U.S. Congress, Office of Technology Assessment, *World Population and Fertility Planning Technologies: The Next 20 Years*, OTA-HR-157, Washington, D.C., February 1982.
26. U.S. Congress, Office of Technology Assessment, *The Information Content of Premanufacture Notices: A Background Paper*, OTA-BP-H-17, Washington, D.C., April 1983.
27. U.S. Department of Health, Education, and Welfare, National Institutes of Health, "Guidelines for

Research Involving Recombinant DNA Molecules," *Federal Register* 41:27911-27922, July 7, 1976.

28 U.S. Department of Health and Human Services, Food and Drug Administration, "Minutes of the Industrial Practices Subcommittee Meeting," (Sept. 4, 1980), reprinted in *Recombinant DNA Research* 6:492-496, 1981.

29 U.S. Department of Health and Human Services, Food and Drug Administration, "Notice of Memorandum for Understanding with the United States Department of Agriculture Animals and Plant Health Inspection Service," *Federal Register* 47:26458, June 18, 1982.

30 U.S. Department of Health and Human Services, Food and Drug Administration, "Proposed New Drug and Antibiotic Regulations," *Federal Register* 47:46622-46663, Oct. 19, 1982.

31 U.S. Department of Health and Human Services, Food and Drug Administration, National Center for Drugs and Biologics, Office of Biologics, "Points to Consider in the Manufacture of *In Vitro* Monoclonal Antibody Products Subject to Licensure," Bethesda, Md., June 1983.

32 U.S. Department of Health and Human Services, Food and Drug Administration, National Center for Drugs and Biologics, Office of Biologics, "Interferon Testing Procedures: Points to Consider in the Production and Testing of Interferon Intended for Investigational Use in Humans," Bethesda, Md., July 1983.

33. U.S. Department of Health and Human Services, Food and Drug Administration, National Center for Drugs and Biologics, Office of Biologics, "Points to Consider in the Manufacture of Monoclonal Antibodies for Human Use," Bethesda, Md., July 1983.

34. U.S. Department of Health and Human Services, National Institutes of Health, "Guidelines for Research Involving Recombinant DNA Molecules," *Federal Register* 47:17180-17198, Apr. 21, 1982.

35. U.S. Department of Health and Human Services, National Institutes of Health, "Program To Assess the Risks of Recombinant DNA Research; Proposed Second Annual Update," *Federal Register* 47:55104-55109, Dec. 7, 1982.

36. U.S. Environmental Protection Agency, "Proposed Data Requirements for Pesticide Registration," *Federal Register* 47:53192, Nov. 24, 1982.