value in the development of vectors with a wide host range.

There are several such vectors currently in use, including the 20 kb vector pRK290, and the pKT series; however, these are restricted to *E. coli* and related bacteria (e.g. *Salmonella*). Bifunctional vectors, such as those for *E. coli-Bacillus subtilis* and *E. coli-Saccharomyces cerevisiae* transfers, have also been developed. Both the gram positive bacterium *B. subtilis* and the yeast *S. cerevisiae* are favored as industrially useful microorganisms.

The communication from Kado's laboratory in this issue of BIO/TECHNOLOGY (p. 269) describes the construction of new, broad host range gene cloning vectors for the *Enterobacteriacae* (*Klebsiella pneumoniae, Serratia marcescens, Erwinia* spp.), *Rhizobiaceae* and *Pseudomonas* species. The vectors were derived from the IncW plasmid pSa, originally developed for use in *Agrobacterium* species. Kado and coworkers have succeeded in constructing a set of versatile vectors that can be used for genetic analysis and gene cloning in a large number of gram negative bacteria. ◪

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GOVERNMENT POLICY

REGULATORY TRENDS FOR BIOTECHNOLOGY PRODUCTS

The legal issues surrounding federal agency regulation of commercial applications of biotechnology have, until recently, taken a back seat to those associated with patent and intellectual property rights. As the scale-up from laboratory setting to large-scale production continues, biotechnology-derived products are starting to reach the marketplace and questions regarding federal regulation become increasingly important.

What are the regulatory issues? Which agencies are involved? The problems and issues involved with using biotechnology to prepare consumer products arise not so much because the technology is unique, but because the applicable law is ambiguous. The primary agencies involved are the Food and Drug Administration (FDA), which regulates food ingredients, drugs (*e.g.*, hormones), human biologics (*e.g.*, vaccines), and medical devices such as *in vitro* diagnostics, and the United States Department of Agriculture (USDA), which regulates animal biologics. The Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration (OSHA) also have significant regulatory authority.

Although biotechnology can produce totally new products that may pose unique regulatory questions, the regulatory issues that are relevant now surround the use of biotechnology as a new method for manufacturing products already on the market. These questions include: what is the regulatory status of FDA- and USDA-cleared products now manufactured using biotechnology? What are OSHA's powers to regulate industrial applications of biotechnology in the workplace? What are EPA's powers to protect the environment? These questions were addressed at a conference entitled "Biotechnology and the Law: Regulatory Strategies for Marketing Biotechnology-Derived Products" that was held last March in Washington, D.C.

General Legal Principles

The burdensome nature of an agency's regulatory powers and the related notion of ease of entry into the marketplace are integrally related to a federal agency's premarketing clearance powers. Regulation often requires a large amount of time, effort, and funds, and usually results in a significant delay in reaching the marketplace. On the other hand, obtaining premarketing clearances creates a certain degree of market protection, almost a "limited monopoly," but it is no substitute for patent protection.

FDA, USDA, and EPA all have considerable authority to oversee biotechnology via their premarketing clearance powers. EPA administers a comprehensive system of environmental regulation. EPA's jurisdiction under the Toxic Substances Control Act (TSCA) enables EPA to regulate process and product hazards and provides for the regulation of all chemicals, existing and new. OSHA has authority under the Occupational Safety and Health act of 1970 to regulate hazards in the workplace associated with biotechnological processes or products, but it has no premarket clearance authority. Its powers to regulate industrial applications of biotechnology are rather limited, at least until a significant risk of harm can be demonstrated[1].

FDA's or USDA's premarket clearance authority depends upon the type of commodity. Determining the appropriate regulatory class of a product is the first step towards ascertaining the costs involved in marketing. Table 1 shows how different types, or classes, of products are regulated by FDA and USDA.

The regulatory class of a product is often quite clear, but intended uses of a product can alter its status. For example, foods such as beef and corn added to stew become "food additives" that may require FDA premarketing clearances. While use of biotechnology does not ordinarily (and should not) alter a product's regulatory class, it may affect a product's regulatory status. If a product manufactured by one method is cleared by FDA, an "identical" product is not automatically cleared when a new method of manufacture is utilized.

For example, an approved drug made by biotechnology is still a drug, but it does not retain "approved" status, *i.e.* it will require new premarketing approvals. Whether new clearances must be obtained when a nonconventional method of manufacture is employed depends on the type, or class, of product because drugs, biologics, medical devices, and food ingredients are regulated differently.

Regulatory Classes of Products

The legal class to which a product is assigned often depends on four considerations: the claims made for the product; its mechanism of action; ingredients; and safety. The method of manufacture is usually not relevant.

The first criterion, which is often the most important, involves the intended use of the product. This is usually gleaned from advertisements and information printed on product labels. Statements avowing either the safety or efficacy of a product generally give rise to its classification as a drug. A good example of this principle is FDA's recent action against the manufacturers of starch-blockers, which are alleged to prevent the digestion of starch and to help in weight reduction. Manufacturers of these products claimed that they were foods, which do not require premarketing clearances under the FD&C Act. However, FDA seized the products as unapproved new drugs, which do require premarketing clearances[2]. The court decided that statements such as "totally natural and safe," and "absolutely safe and exceptionally effective . . . no side effects," which were used in the promotion and labeling of the products, were drug claims. The court also noted that foods are consumed for either taste, aroma, or nutritional value. Since starch-blockers were not used for any of these purposes, they were drugs subject to premarket approval.

The mechanism of action of a product can also determine its legal

class. For example, the FD&C Act specifies that a device cannot achieve any of its principal intended purposes through metabolism or chemical action within or on the body of man or animals. Interestingly, the FD&C Act does not specify how drugs or foods function, although there is some language defining drugs as articles (other than food) intended to affect the structure or function of the body of man or animals[3].

The nature of the ingredients used in a product does not usually determine the product's class. For example, manufacturers unsuccessfully argued that the starch-blocking compound was derived from foods; therefore, it was a food, too. However, in some cases it is quite clear that what is in a product is just as important as its intended use.

A recent case involved a product containing vitamin A and interferon that FDA seized as an unapproved new drug. The manufacturer argued that the product was food[4]. Although the court never decided the issue of the appropriate class of the product, it seems unlikely that a product containing interferon can be classified as a food because interferon is typically used for drug purposes, the curing of disease. Fluoride is another example of an ingredient that can make a product containing it fall within the definition of a drug.

Finally, it is important to realize that when determining the legal class of a product, an overriding concern is its safety. In the starch-blockers case, the court was disturbed by the fact that use of the product could have allegedly serious side effects. Numerous legal cases stand for the proposition that courts will side with the agency charged with protecting the public health, and impose premarketing clearances by classifying a product as a new drug.

Premarket Clearance Authority of FDA and USDA

Premarketing clearances are required for all "new" food additives, human or animal drugs and biologics, and medical devices. Therefore, determining whether a product is "new" is critical to determining how quickly it can be marketed. Not all products require clearances from FDA before they can be marketed. No clearances are needed for animal or human foods, although such products are subject to purity and quality standards.

"Food additives" are regulated by the FDA on a generic basis. Once a food additive regulation is promulgated, *all* manufacturers of that additive may market it without obtaining individual clearances, provided the manufacturer's specific formulations satisfy the regulations. Marketing clearances are required for new additives unless they are generally recognized as safe (GRAS) or prior-sanctioned. New methods of manufacture can affect the legal status of GRAS ingredients[5]. Fructose, which is considered GRAS, would therefore probably require premarketing clearances as a new food additive if it is made by genetically engineered organisms.

FDA's authority over human medical devices, which include human *in vitro* diagnostics, depends upon the class of the device. There is a notification requirement (510(k), based on the section of the FD&C Act that requires the submission), which gives FDA limited premarketing-type approval powers[5]. Class I and II devices, such as the current diagnostic tests for infectious mononucleosis, are regulated generically. Class III devices, such as screening tests for gonorrhea, are regulated on a product by product basis.

Biotechnology probably has its greatest commercial impact in the area of human devices because monoclonal antibodies are now being used as diagnostics for many diseases. Animal and human *in vitro* diagnostics are, by definition, medical devices regulated by the FDA, unless they contain biologics (*e.g.* antibodies) and are used for diagnosis of animal disease. In this case they are regulated by USDA.

Agency Policies on Biotechnology-Derived Products

Until recently, no federal agency had a policy on biotechnology-derived products that might affect the scheme of regulation discussed above. Last year a Memorandum of Understanding (MOU) was executed between FDA and USDA regarding responsibilities of each agency for regulating animal biologic products as biologicals or drugs[6]. A Committee was formed to address the status of products derived from biotechnology.

The only major decision out of this committee—and it remains a tentative decision—appears to be that interferon used in the treatment of animal diseases is not an animal biologic regulated by USDA, but is an animal drug regulated by FDA. This decision turns on a narrow reading of the statutory and regulatory definitions for an animal biologic, a discussion which is beyond the scope of this article. For now, suffice it to say that I believe that this position is unwarranted and inconsistent with both past and present FDA practices[7,8].

A few years ago FDA established a Recombinant DNA Coordinating Committee composed of representatives of various bureaus and offices, such as the Offices of General Counsel and Regulatory Affairs. On January 7, 1983, a paper entitled "Regulating Recombinant DNA Products," was released by this committee. It states that products derived from recombinant DNA will need clearance from FDA even if the products are identical in structure to previously cleared or naturally occurring products. The amount of data required will depend on factors such as the proposed use of the product, whether it is identical to a previously approved product, how long it is to be administered to patients, the previous clinical experience with conventionally produced products, and the applicant's clinical experience with recombinant DNA-derived substances.

The effect of the new policy seems to be to require full clinical testing of *all* rDNA drugs, even if they are identical to conventionally-produced versions. The rDNA produced hu-

TABLE 1 Jurisdiction of FDA and USDA over Biotechnology-Derived Products

Product	Agency	Office[1]	Statute[2]
Human			
Drugs	FDA	Office of Drugs	FD&C Act
Biologics	FDA	Office of Biologics	PHS Act
Radiolabeled biologics	FDA	Office of Drugs	FD&C Act
In vitro diagnostics	FDA	Office of Devices	FD&C Act
Food and food additives	FDA	Bureau of Foods	FD&C Act
Animal			
Drugs	FDA	Bureau of Vet. Med.	FD&C Act
Biologics	USDA	APHIS	VSTA
In vitro biologic diagnostics	USDA	APHIS	VSTA
In vitro diagnostics	FDA	Bureau of Vet. Med.	FD&C Act
Foods and food additives	FDA	Bureau of Vet. Med.	FD&C Act

[1]Animal and Plant Health Inspection Service (APHIS) is part of the United States Department of Agriculture (USDA); the Food and Drug Administration (FDA) is composed, in relevant part, of the National Center for Drugs and Biologics, the National Center for Devices and Radiological Health, and the Bureaus of Food and Veterinary Medicine (Vet. Med.).
[2]FD&C Act: Food, Drug, and Cosmetic Act. PHS Act: Public Health Service Act. VSTA: Virus, Serum, Toxin, and Analogous Products Act of 1913.

man growth hormone is now undergoing full clinical tests to obtain FDA approval. FDA required a new application because the rDNA product differs by one amino acid from the conventionally-derived version, which is obtained from cadavers. In the context of the new policy, rDNA derived human growth hormone that was identical to the conventional product would still require the same full clinical testing. The obvious effect of this policy is to increase the cost of marketing rDNA products.

The major thrust of the new policy is in the human drug area; it is not really a new policy in one sense: FDA requires "new applications" for previously approved drugs that are now manufactured by a different method. However, the extent of FDA's authority to require new clearances for drug products manufactured by a new method remains unclear. A recent decision of the Supreme Court[9] indicates that if duplicates of drugs cleared by the FDA are bioequivalent, then new clearances *may* not be required under the FD&C Act, even if the copies contain different active ingredients. How a new method of manufacture such as genetic manipulation affects the approved status of a drug remains unclear under this decision.

It is also not yet clear how this new policy will affect other types of products within the jurisdiction of FDA. If broadly interpreted, this policy could affect the status of previously cleared food additives now made by biotechnology. For example, amino acids, which can be used as dietary supplements or food additives, are now cleared without specification to their method of manufacture. Amino acids produced by rDNA methods would have to undergo safety testing to obtain new FDA clearances.

The National Institute for Occupational Safety and Health (NIOSH), which makes recommendations to OSHA regarding safe exposure levels to substances, did some investigating a few years ago of the potential hazards associated with industrial uses of the rDNA technique. Although NIOSH's recommendations in this area were to be submitted to OSHA and to provide a basis upon which to develop a regulatory policy, nothing ever materialized when the Reagan Administration took over. No policy statements seem likely in the near future, at least until there is adequate reason to worry about hazards from biotechnology.

EPA has been relatively silent in this area over the past few years. The Office of Research and Development of EPA has conducted some environmental risk assessments[10] and the Office of Exploratory Research has published reports on future environmental problems in relation to the rDNA technology. Prior to his departure, John A. Todhunter, former EPA Assistant Administrator for Pesticides and Toxic Substances, specifically called on the Toxic Substances Advisory Committee to assess implementation and recommend action EPA should take under the TSCA. Quite possibly, EPA will be intimately involved with the regulation of biotechnology, not only under TSCA but also under numerous other environmental statutes that the Agency administers[11].

Strategies for Marketing

In light of the foregoing discussion of agency policy statements and the extent of FDA and USDA regulatory power over various types of products, it is obvious that the quickest way to market a product made by biotechnology is to prepare one that requires no premarketing clearances. Where this is not possible, the easiest way to get on the market is to manufacture a product that has been previously cleared by FDA. The present discussion focuses on biotechnology-derived products in two broad categories: new products and old products made by a new method of manufacture. In general, it is easier to market the latter than the former.

Biotechnology-derived copies of products that are regulated generically can be marketed with relative ease: no premarket clearance requirements exist. Animal and human drugs that have been previously marketed and are now prepared by biotechnology should, in theory, be nearly as easy to market. However FDA's recent statements—that the use of biotechnology may make a previously marketed drug a "new" drug that requires new, full clinical studies for approval—cast considerable doubt on this proposition. Abbreviated applications to expedite FDA approval may therefore not be possible. Copies of approved animal and human biologic products are the most difficult to market, because every manufacturer must obtain separate approval and abbreviated application procedures are usually not available.

Ease of entry into the marketplace for new, biotechnology-derived products also depends upon the type of article. Foods and non-biologic animal devices, *i.e.*, those devices that do not contain antibodies as components, require no clearances at all and rank at the top of the list. Food additives are next, primarily because new food additives usually require less testing than new class III devices or new drugs.

Biotechnology-derived biologics, such as a foot and mouth disease

vaccine produced via genetic engineering, are probably marketed more easily than new human or animal drugs and human biologics falling under the jurisdiction of the FDA, because the requirements of USDA are generally less rigorous than those of FDA. New animal or human drugs and human biologics, therefore, fall at the bottom of the list because extensive clinical and nonclinical information is usually required before FDA will approve them.

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ASIAN BIOTECHNOLOGY

BIOLOGICAL PEST CONTROL: NEW CHINESE EXPORT

The People's Republic of China (P.R.C.) is increasing its reliance on biological pest control methods (BPC) to contain insect pest populations and boost agricultural production. The methods include rearing and releasing parasitic arthropods, application of fungal and bacterially derived insecticides, spreading insect viruses, release of selected frogs and ducks to eat harmful pests, and use of pheromones and hormones to attract injurious insects.

China's use of BPC is not new: the earliest records of this technique date from 324 B.C.[1] The current stress on biological control technologies is due to both economic pressure and China's growing concern with the environment. Chemical insecticides are used in China, but reliance on foreign sources of supply for many of these substances, combined with China's lack of foreign exchange, limit their availability. A Chinese report on the use of *Trichogramma* sp.[2], a small parasitic wasp, against cotton bollworm, showed that this technique costs 88.5 percent less than standard insecticide treatment.

Prof. Li Liying, Director of the Guangdong Entomological Institute in Guangzhou, and a leading figure in BPC research in China, wrote in a recent report that biological control "claims precedence over all others. . ."[3]. In 1978 alone, China subjected more than 21 million cultivated acres to BPC. According to recent published accounts from the U.S. Department of Agriculture's China Program,[4] this number is steadily increasing.

China's BPC technology is based on its system of labor-intensive agricultural methods and localized production sites. Little of the work of raising and distributing beneficial organisms is mechanized. Even China's most prestigious research institutions have had to fabricate their own equipment for pest control research. Although airplanes are used in some areas for pest control product delivery, and China maintains Y-11 transport aircraft for agricultural use,[5] the small size of most agricultural fields precludes widespread use of this method.

International Organism Exchanges

Many of the organisms currently raised in China for biological pest control were imported from the Soviet Union and Eastern European countries in the 1950s. Since 1972, China has received biological control organisms from Western Europe, South America, Canada, and the U.S. According to Dr. Huai C. Chiang, Professor of Entomology at the University of Minnesota, "Recent developments (in China) have been enhanced through international exchanges." Official exchanges between the U.S. and China began in 1979[4] when China received two species of insects, two species of fungi, one bacterial species, and six virus types via official channels.[1] In 1982, China received two species of arthropods, six virus types, and one species of nematode worm from the U.S.[6] International cooperation is not limited to exchange of organisms: China and Japan recently signed an agreement for joint research on agricultural antibiotics.[7]

International exchange and cooperation in BPC does not benefit only the Chinese. The developed nations, especially those in the western hemisphere, will probably gain more from the relationship with China than the

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Small Trichogrammid wasps are used for biological pest control in China. The wasps are parasites in the eggs of many harmful insect species.