Martin Terry
Vice President for Scientific Activities
Animal Health Institute

Animal Pharmaceuticals

UNDEFINED TURF

The Food and Drug Administration (FDA) regulates animal drugs under the Food, Drug and Cosmetic Act, while the U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA/APHIS) regulates animal biologicals under the Virus-Serum-Toxin Act. But the question of which agency has jurisdiction to regulate a given animal health product is not always a totally obvious one. The regulatory definition of a biological is in need of updating to clarify the status of some of the compounds being developed through biotechnology. Particularly difficult to classify are those compounds which occur endogenously, modulate the immune response and have pharmacological properties. A classic example of this sort of regulatory ambiguity can be seen in the handling of the interferons which are regulated as *biologicals* (by FDA's Center for Biologics Evaluation and Research) *for human use*, but are regulated as *drugs* (by FDA's Center for Veterinary Medicine) *when labeled for use in animals.* This disparity has more to do with interagency politics than it does with the pharmacological/immunomodulatory effects of interferons. The Animal Health Institute (AHI) is currently working on a proposal to amend the regulatory definition of a biological, with the object of providing a more adequate taxonomy of drugs vs biologicals—which would *ipso facto* determine which agency should have jurisdiction to regulate a given substance or product.

PRODUCT VS PROCESS AND THE GLASS FOURTH HURDLE

A cornerstone of the final "Scope" policy statement of the Office of Science and Technology Policy as published in the *Federal Register*, February 27,1992, is the notion that regulatory oversight is appropriately applied in direct proportion to the *risk* associated with a given *product per se,* independent of the *technology* employed in the manufacturing *process.* Interestingly, neither objective product risk assessment nor concern with the nature of the manufacturing process has occupied center stage in the controversy surrounding bovine somatotropin (BST), the first high-profile product of biotechnology to be developed as an animal drug.

Since FDA finished its food safety evaluation of BST in 1986 and pronounced that there were no human food safety issues arising from the

use of BST in lactating dairy cattle (Juskevich and Guyer, 1990), the public debate has focused on possible economic and social effects of the anticipated widespread adoption of the use of BST by the dairy industry. Questions have been raised and projections made as to the magnitude of the effects of widespread BST use on volume of milk production, milk prices, dairy herd size and the continued viability of marginal, inefficient dairy operations.

FDA cannot legally take such socioeconomic considerations into account in the premarket drug approval process; animal drugs must be evaluated on the basis of the objective criteria of safety and efficacy. However, FDA does not operate in a political vacuum and in a situation where heated political debates on the socioeconomic aspects of a new animal drug run concurrently with the regulatory evaluation of the drug, it is hard to believe that the agency would not be affected to some degree in its deliberations on the drug. At the very least, the political heat radiating from the socioeconomic issues can be seen to make the agency even more cautious than usual in its evaluation of the safety and efficacy data on the drug—which would logically result in a delay in the approval process.

Moreover, while the effects of socioeconomic criteria on the regulatory process may be subtle and unofficial at the federal level, they can be blatant and most official at the state level, as evidenced by the current legislative moratorium on the use of BST in Maine.

DOORS VS WINDOWS

Another issue which is by no means unique to biotechnology products, but which, as a matter of historical fact, emerged as the subject of public controversy in the course of the ongoing BST debate, is that of *regulatory transparency.* In 1986 in the UK, headlines appeared about "secret trials" being conducted with BST on undisclosed farms, with innuendoes of collusion between the animal health companies and the British Ministry of Agriculture. What, in fact, was happening was that animal health companies were field-testing a product for efficacy—the human food safety of the product having already been established to the satisfaction of the regulatory authorities—in accordance with the pertinent regulations, in exactly the same way as hundreds of other animal health products had been tested previously. The brouhaha arose, not because BST was receiving any favored treatment by the British government—that was clearly not the case—but rather because the public was totally unaware of the regulations and legal procedures routinely used in the testing and approval of animal drugs—until the BST critics sought to portray those procedures as some sort of conspiracy against the public.

At the heart of the transparency issue is a conflict between the public's "right-to-know" and a drug sponsor's legal right to confidential treatment of proprietary information on a product including the details of the tests conducted to demonstrate the safety and efficacy of the product in the regulatory approval process.

In the U.S., the Food, Drug and Cosmetic Act provides that data which are submitted on a new animal drug by the drug sponsor will be evaluated on a confidential basis by FDA. The first regulatory hurdle which must be cleared in the drug approval process is that of establishing human food safety. Only when a new animal drug has been sufficiently evaluated and found to be safe from the point of view of humans consuming food produced by animals treated with the drug, may FDA approve an Investigational New Animal Drug Application (INADA) which authorizes the drug sponsor to conduct tests to demonstrate the efficacy and target animal safety of the drug. In the FDA-monitored field trials conducted under an INADA, the issue of the safety of the food derived from the test animals has already been resolved by FDA. Thus, in terms of human food safety the drug is no longer an "experimental drug." At the INADA stage, a drug is actually "experimental" only in regard to its efficacy and its safety *to the target animal* at dosages intended for commercial use. The food produced by the animals involved in such testing is as safe as any other food produced with fully approved new animal drugs. Claims that the public is being put in jeopardy through exposure to food produced with an "experimental (INADA) drug" are ill-founded, and usually mischievous.

Yet there is a point of view which says that even if FDA says a product or technology is safe, the public has a right to know whether the food in commercial channels was produced with that product or technology. Here the question of *labeling* rears its head and labeling is a highly controversial issue.

In principle, no one should object to providing the consumer with as much objective, nonproprietary information about food products as the consumer has patience to read. However, in the reality of commercial food production and marketing there are some difficulties involved in routinely providing certain types of information on the label of a food product. Let us consider, for example, the very topical notion of positively labeling a food product with something like: "Produced with xenophobein, a hormone derived from recombinant DNA technology." Let us say that this imaginary protein called "xenophobein" has been found by FDA to pass all the rigorous regulatory tests for human food safety and that food produced with xenophobein is analytically identical to food produced with traditional technologies. In such a case, what are the consequences of putting the above-quoted information on the label of food produced with xenophobein? Four come immediately to mind:

1. Such labeling contributes *nothing to* the consumer's knowledge in terms of safety or nutritional information, given that there is no objective difference between food produced with xenophobein and food produced without it. So, in a scientific sense, such labeling is gratuitous and of *no* consequence.

2. To insist on detailed labeling as to the technology by which a food is produced when the food itself has been found by FDA to be safe, is essentially

to discount FDA's safety evaluation process. If we accede to demands that consumers should be given the opportunity to make their own safety assessment (presumably on the basis of data purveyed by such prestigious scientific journals as *The Wall Street Journal),* the logical conclusion is that product labeling should be sufficient to allow consumers to protect themselves through the exercise of "informed" choice. But in that case FDA's evaluation would be, at best, redundant and, at worst, in disagreement with the consumer's personal evaluation. We could just as well dispense with the services of FDA and revert to a system of exhaustive labeling and *caveat emptor.*

It seems to me that, for all FDA's imperfections.—and AHI is traditionally one of FDA's most vocal critics—we as a society are better off with a government-run agency making regulatory decisions on the basis of expert scientific evaluation, than we would be in a system of "every man [sic] his own regulator," where some would demand that an encyclopedia of product information and manufacturing data be attached to each can of pork 'n beans and the role of the agency would be reduced to that of an editor of encyclopedias.

3. As my colleagues in the European Commission learned when they proposed positive labeling of beef produced with hormones as a solution to the European hormone debate in the midi 980s, the use of emotive terms like "hormone" in labeling is likely to scare, rather than objectively inform, consumers. (That, of course, is exactly the effect desired by many who advocate such labeling, as their interest is not in accurately informing consumers, but rather in politically motivating consumers through the manipulative use of "hot" language which serves to obfuscate rather than to educate.) Even with the best of intentions, what is intended as a neutral statement of fact on a label can be all too easily misinterpreted as a warning.

4. Labels generally are, of necessity, minor masterpieces of succinctness. Space on a label is available only at a cost and any statement that did not convey concrete information as to the safety or nutritional value of the contents of a food package would carry uncompensated added costs which would increase the cost of the product to the consumer without providing a benefit. [1]

I would emphasize that the above considerations apply only to *positive* labeling, e.g., "This product was produced with xenophobein." There are no such objections to *negative* labeling, e.g., "This product was produced without xenophobein."Though the fact remains that the product produced without xenophobein is identical to that produced with xenophobein—and therefore the negative labeling is scientifically as meaningless as positive labeling would be—the option of negative labeling allows consumers to exercise choice in the process by which their food is produced.

Negative labeling has the advantage of being equitable to all parties involved in food production and consumption. If there is sufficient demand

for a product produced by an "alternative" (which generally means low-tech, high-cost) technology—i.e., if producers find that it is commercially viable to exploit a niche market based on a perceived consumer preference for food produced without the use of a "mainstream" (generally high-tech, low-cost) technology—then by all means "let a thousand flowers bloom" in the marketplace. Let consumers decide with their checkbooks which products best satisfy individual preferences—whether those preferences be based on cost, safety, nutritional quality, aesthetics, ideology, or a combination of factors. Let producers decide which markets they want to cater to, matching production technologies with consumer preferences—as determined by the extent to which consumers are in fact willing to pay premium prices for products produced with the less efficient technologies.

COMMERCIAL PROMOTION VS POLITICAL SELF-DEFENSE

Of current concern in the regulation of animal pharmaceuticals—and of particular relevance to those derived from biotechnology—is the issue of pre-approval "promotion" or defense of a product by the manufacturer while the product is still under evaluation by PDA. The agency has defined "promotion" so broadly as to impose very narrow limitations on the information that can legally be conveyed to the public by a manufacturer about a product in the pre-approval phase. The AHI has taken a quite different position on what kinds of activities constitute commercial promotion—as opposed to the pre-approval defense of a product in response to political attacks intended to prevent its approval.

The AHI view is that the severe limitations on the dissemination of information which FDA has sought to impose on AHI and its members are not dictated by the relevant regulations, are inconsistent with Administration policies to remove impediments to the development of new technologies and are seriously at odds with AHI's and its members' constitutionally protected rights to protect their property interests fully in the political arena. Negotiations are underway to attempt to resolve this dispute which has far-reaching implications for the application of biotechnology in animal agriculture.

IMPEDIMENTS TO DRUG APPROVAL VS THE THREAT OF SNAKE OIL

The last issue I would like to touch on, namely, the need to revisit the statutory efficacy standard for animal drugs, is in a sense a by-product of the current debate on extra-label drug use. It is not unique to biotechnology products, but it has coincidentally arisen as a major regulatory issue at the time when the first biotechnologically produced animal drugs are in the latter stages of the FDA approval process—which is to say, at the time when these biotechnology products are undergoing efficacy testing.

The efficacy standard for animal drugs, as set forth in the Food, Drug and Cosmetic Act, is relatively simple and straightforward. In ordinary language, FDA must require "substantial evidence" that a product is effective

for the purpose for which it is intended, i.e., an animal drug cannot be approved by FDA until it has been shown not to be "snake oil." The "substantial evidence" required is ordinarily in the form of "adequate and well-controlled studies."

Unfortunately, this reasonable, bare-bones efficacy standard as set forth in the statute has undergone a sea-change of agency interpretation over the last few decades. Regulatory barnacles and mineral accretions have built up in the form of ever-more-complex policies for efficacy testing requirements. The problem has now reached such proportions that it often costs more for an animal drug sponsor to conduct the efficacy studies required for FDA approval than it does to conduct the *safety* studies which have traditionally accounted for the major portion of the cost of product development.

Particularly onerous to sponsors seeking regulatory approval of new animal drugs is FDA's current policy to require "optimal dose" titration studies, in which a number of doses (the majority of them irrelevant to clinical reality) are tested for efficacy, in order to determine the lowest dose which is adequately effective. Clearly this requirement adds greatly, and unnecessarily, to the cost and time required to get a drug approved. But it also has the additional long-term disadvantage of freezing the label dose at a level which may itself be clinically irrelevant by the time the drug has been used in the field for a few years. (For a good example of the latter problem, consider penicillin which is now universally acknowledged to be virtually useless in veterinary medicine at levels less than three times the once "optimal" dose which is still the only dose on the product label.)

To address these problems, AF1I and the American Veterinary Medical Association (AVMA) have filed a Citizen Petition proposing that FDA approve dosage ranges and eliminate the requirement for optimal dose titration in efficacy testing. The proposal applies only to new animal drugs which have adequate safety data packages and which would be restricted to use by or on the order of a licensed veterinarian. The statutory deadline for FDA to respond to the Citizen Petition passed silently several weeks ago. In light of the recently launched AVMA legislative initiative to legalize extra-label drug use by veterinarians, this silence on FDA's part could be pivotal. If FDA is perceived as being unable to respond positively to proposals submitted in a regulatory mode to streamline current policies on efficacy testing, that would surely be interpreted by some in the industry as an indication that legislation is the only available remedy.

Regardless of whether it is eventually achieved through regulatory channels or through Congress, streamlining the efficacy testing requirements for animal drugs has clear advantages. It would free up agency resources to devote to the crucial process of safety evaluation of new animal drugs. It would remove a major economic disincentive that currently discourages drug sponsors from seeking broader label indications for new drugs. And it would have a positive impact on the rate of approval of new animal drugs (including bio-

technology products) which would mitigate the crisis in drug availability which currently besets animal agriculture.

REFERENCES

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