Regulation and application of biotechnology products for use in veterinary medicine *

J.W. GLOSSER **

Summary: The author outlines legislation in the USA and the role of the Animal and Plant Health Inspection Service in licensing vaccines and diagnostic products produced by biotechnological procedures. Use of diagnostic reagents for rapid tests shows great promise, though precautions are needed to prevent their misuse.

KEYWORDS: Biological products - Biotechnology - Legislation - Licensing - Rapid tests - USA - Vaccines.

In pursuing the dynamics of the marketplace of biotechnology in animal health and the impact that regulatory issues might have today, I would like to tell you how the United States Department of Agriculture (USDA) is responding to some of the regulatory challenges that the “new biotechnology” has posed. I will briefly review our policy on and authority for regulating veterinary biological products produced through biotechnology; the challenges posed by the persistent myths surrounding biotechnology; the commercial and agricultural impact of biotechnology; our procedures for and experience in the licensing of biological products; and, finally, I will take a close look at the promise we have seen in one class of these products.

Our goal at USDA is to protect American agriculture through regulations based on firm scientific principles which are clear, precise, and relevant in today’s changing technological world. Simply stated, the role of USDA is to foster a regulatory climate which encourages the innovation, development, and commercialization of beneficial new agricultural products derived from biotechnology, while implementing responsible regulatory policy that limits potential or real risks. However, we as regulators and scientists must recognize that not only must these products be safe and efficacious, but the public must have confidence in their safety.

On 31 December 1984, the Department published a statement of policy for the regulation of biotechnology and products (8). The policy stated:

1) Biotechnology products will not differ fundamentally from products produced by conventional methods;

2) The existing statutory framework is adequate to regulate biotechnology;

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3) Genetically-engineered organisms or products will not be regulated simply because of the process by which they were produced.

The Virus-Serum-Toxin Act of 1913 (VSTA) gives USDA the authority to regulate all veterinary biologics imported into the United States or shipped or delivered for interstate shipment (7). Recent amendments contained in the Food Security Act of 1985 extended this authority to products shipped within states or exported, and gave USDA such additional enforcement mechanisms as the power to detain and seize products (1).

The Veterinary Services (VS) of the Animal and Plant Health Inspection Service (APHIS) issue US Veterinary Biological Product Licenses upon satisfactory completion of all requirements including review and acceptance of labels. Products imported into the United States must have a permit issued by the Secretary of Agriculture. The regulations for veterinary biologics are found in Title 9, Code of Federal Regulations (CFR), Parts 101 to 117.

Veterinary biological products produced by recombinant DNA (rDNA) methods are evaluated on a case-by-case basis using the same stringent standards for product safety, purity, potency, and efficacy required for licensing of conventionally produced biologics. I will discuss later a classification scheme for recombinant-derived products based on biological characteristics and safety concerns. This scheme was also published as a part of the Final USDA policy statement on biotechnology, 26 June 1986 (9).

APHIS also issues a VS permit for the importation into the United States of biological materials such as cell cultures, monoclonal antibodies, organisms, vectors, or related materials. This authority is granted by the VSTA and the Act of 3 February 1903. USDA issues regulations and takes the measures necessary to prevent the introduction or dissemination of any contagious, infectious, or communicable disease of animals and/or live poultry into the United States from a foreign country, or from one state to another. The importation and interstate shipment of organisms and vectors is regulated under 9 CFR, Part 122.

**MYTHS AND REALITIES OF BIOTECHNOLOGY REGULATION**

In exercising our authority, we have found that one of the principal challenges we face with the advent of new biotechnology involves perception as much as reality. The potential of the new technology can be realized only if we correct the misconceptions and mitigate or eliminate the harmful effects of the myths that have been introduced and nurtured with the unfortunate use of the general term "biotechnology".

Separation of the myths from the real issues also is essential for effectively administering a sound regulatory policy. Only through such a separation can we adequately explain to the public the rationale behind our regulatory policy. In my opinion we have been much too passive or perhaps too preoccupied in reacting to the perceived risks rather than devoting our energies to a fair and objective discussion of what is actually involved with the new technology and what can be expected from the varied biotechnological processes.
If the opportunities of a new technique are so enormous, why should the public be afraid of them? There are two reasons:

1) Anything which is unknown is, a priori, frightening;

2) Biotechnology is extremely complex in concept and execution and, therefore, difficult for laymen to grasp and understand.

In the past, many policy makers were convinced that the fears and anxieties which were associated with biotechnology in public audiences were due to a lack of information; and that scientists had been unable to explain the background, the present state, and the limitations of their new discoveries to the ordinary citizen in clear and understandable terms.

Scientists traditionally demonstrate their results in a methodical, systematic, step-by-step process to explain the pathways and blueprints to other scientists, often allegedly ignoring the man on the street.

Therefore, it seemed reasonable to make every effort to correct this situation by intensive information campaigns which would explain in simple and attractive terms the principles as well as the achievements of biotechnology. It seemed entirely plausible that on the basis of such information, the layman would clearly see the unique opportunities which the new biotechnology offers and that the potential dangers are relatively minor compared to the potential benefits.

In the last few years a number of first-class information campaigns, television programs, tapes and books on biotechnology have been produced. More and more people are informed, but the fears and anxieties have not disappeared. If anything, they have increased. Why?

Sociologists are aware that too much information generates cognitive stress. The amount of information necessary to grasp the importance of biotechnology requires an intellectual effort which is beyond many people. Also, in many instances the benefits of biotechnology have been oversold or exaggerated. Therefore, to avoid the stress of over-information, it is much easier and simpler to follow those who say that anything new which cannot be understood and about which not even the experts can exactly and simply say where it will lead us should be rejected. "The world is bad enough, let’s not make it worse."

As a result, the public relies heavily on myths to form their opinion about complex issues.

Paradoxically, regulators must recognize that the more complex the issue to be regulated, the more the public tends to suspect and distrust the regulatory process rather than the issue itself.

Few issues today are as misunderstood as biotechnology. Some people advocate agricultural biotechnology as the “answer to world famine”, others warn not to let it become an example of “science run amok”, and still others consider the process as “just another tool in the geneticists’ toolbox”.

The first of the myths surrounding biotechnology is that the process is something discrete or homogeneous, a corollary of which would be that there exists a single “biotechnology industry”. This kind of thinking is simple and easy but inaccurate. The term has now become a millstone around the neck of universities, the private
sector, and government. Biotechnology is not a single entity, but instead is an enabling technology with broad applications in many diverse aspects of industry and commerce. As we use the term today, biotechnology includes many different applications. It is the establishment of hybridomas for the production of monoclonal antibodies to be used in diagnosis or therapy. It is the use of recombinant DNA (rDNA) technology for producing a hepatitis B vaccine in yeast, a rabies vaccine in vaccinia virus, and the production of Interleukin II in Escherichia coli. It is also the introduction of increased levels or higher nutritional value of storage protein in soybeans. Also, the use of rDNA technology for the engineering of new microbial pesticides or microbes for ore leaching will provide important future products.

The Domestic Policy Working Group on Biotechnology, which continues the group established under the former Cabinet Council on Natural Resources and the Environment, adopted a broad but useful definition of biotechnology: "the application of biological systems and organisms to technical and industrial processes". This definition demonstrates that biotechnology encompasses the many diverse processes described above. Therefore, biotechnological processes and products are so diverse and have so little in common with one another that it is extremely difficult to construct generalizations about them. Perhaps a more valid and descriptive characterization of biotechnology is: a group of several diverse biological processes that result in good manufacturing practices which are environmentally safe.

A second myth is that the field is new. But biotechnology did not suddenly drop into our laps one or two decades ago. This technology has been with us since before 6000 BC when the Sumerians and the Babylonians exploited the ability of yeast to manufacture alcohol and beer.

As the advances in this technology have increased, so has the interest of government officials and the financial community. The result of this special attention has been the gradual broadening of the definition of "biotechnology" to include a number of techniques which have been used for decades, without the attention they now receive. Products derived from chemical or ultraviolet light, mutagenesis, hybrid plants, and micro-organisms produced through genetic exchange are now often considered objects which should be subjected to new degrees of "biotechnology"-related regulation.

Several factors are responsible for this change, but I believe the principal one which is unduly raising public concern is the use of a single, imprecise term to describe those activities. We must find a means to describe the products to be regulated by the specific properties which led to their study, and not simply apply the term "biotechnology". Thus, biotechnology — including its subset, genetic engineering — is neither a monolith nor is it new, and the newest techniques are certainly extensions of the old. But misconceptions about new biotechnology persist and continue to motivate attempts to treat it as a special case. At conferences like this one, all of us have the opportunity to help dispel such myths and put new biotechnology in its proper perspective.

Another term that has great potential for misinterpretation when discussing the "deliberate release" of genetically-engineered organisms is a review of a product on a case-by-case basis. The Department's use of the term coincides with that used by the Organization for Economic Cooperation and Development (OECD) in its recent publication Recombinant DNA Safety Considerations. In that document, "case-by-case" was carefully qualified to mean: "an individual review of a proposal against
assessment criteria which are relevant to the particular proposal; this is not intended to imply that every case will require review by a national or other authority since various classes of proposal may be excluded”. The OECD qualification of “case-by-case” underscores the important principle that categories of products entailing negligible or trivial risk may be defined so as not to require special governmental review (6).

COMMERCIAL AND AGRICULTURAL IMPACT

In the commercial sector, biotechnology will have its most immediate impact on pharmaceuticals and agriculture generally. Because it directly affects such basic human concerns as food production, health care and energy availability, its implications are indeed worldwide.

Exciting research is underway in agricultural applications to enhance animal productivity and help feed the world population. Control of animal and plant pests and pathogens represents another major opportunity. Soon there will be more and better products to diagnose, prevent and treat animal diseases, to improve animal breeds, or even create new ones.

Currently, some 450 companies are involved worldwide in the production of animal care products through the new technologies: 8% of these are major pharmaceutical or chemical companies; 7% are not classed with the veterinary industries but fit the definition of animal health industry; and 85% are small biotechnology companies or independent research institutes.

A prominent concern of all companies involved in biotechnology is the degree of protection they can obtain over the products and processes they develop. In the United States, this protection takes two main forms: patents and trade secrecy. APHIS gives careful attention to the matter of “confidential business information” in its handling of license applications.

In the veterinary market, an impressive array of production will be forthcoming due to the processes of biotechnology, ranging from therapeutics, biologics, and transgenic or phermic animals to diagnostic reagents.

A group of hormone-like molecules which has received considerable attention from the biotechnology industry is the interferons. As glycoproteins, they have the effect of regulating the immune response. Interferons have shown some promise in preventing viral infections, and some evidence suggests they may be effective in checking certain kinds of infections and cancers. These claims could not be clinically substantiated until recently, when large amounts of interferons became available through genetic engineering.

NEW VACCINES

One of the most important implications of biotechnology is in the new generation of vaccines now emerging, which differ from conventional whole-agent vaccines.
Although living-attenuated or killed whole-agent vaccines are highly effective for many diseases, they sometimes produce allergic side reactions and acute or slowly progressive disease. Also, they do not always immunize against all strains of a pathogen, and they often need to be refrigerated, making them difficult to use in some parts of the world.

The new vaccines not only solve many of these problems, they also offer the possibility of vaccinating human beings and animals against a much broader range of diseases. They are safe, stable, effective. Abundant quantities can be produced inexpensively. A group called "subunit vaccines" is comprised of the surface proteins, or segments thereof, of infectious agents produced artificially by molecular cloning or organic synthesis.

Recombinant-derived vaccines are being developed to protect against such diseases as vesicular stomatitis, bluetongue, anaplasmosis, porcine and canine parvoviruses, bovine papilloma, fowl plague, influenza, rabies, feline leukemia, rinderpest and Rift Valley fever.

Producing vaccines against bacterial and parasitic pathogens is more difficult, of course. But genetic engineering is being successfully applied to prepare protein vaccines against bacterial diseases. For example, a cloned vaccine is available to protect animals against _E. coli_ diarrhea in at least one European country.

Now the new technological procedures are being expanded to produce veterinary biologics.

Genetically-engineered vaccines have their highest potential for acceptance in the veterinary market. This is because of the high cost of disease to the livestock industries — some $80 billion per year worldwide.

The world market for FMD vaccine, for instance, is larger than that for any other vaccine, including human products. Productivity losses directly attributable to the disease are estimated at 25%, with the cost estimated at $50 billion annually. More than $1 billion a year is now spent on conventional FMD vaccines.

Because they are not sensitive to temperature, subunit vaccines are suitable for use in countries where they can be stored and even mishandled without loss of efficacy.

In the case of embryo sexing, polyclonals are giving good results for pregnancy tests. Monoclonal antibody tests for pregnancy and fertility will have greater specificity and no doubt worldwide appeal.

Growth hormones produced by genetically-engineered micro-organisms also have an exciting potential in agriculture. Dairy cows injected with growth hormones may increase their milk production by up to 40%. The US market is estimated at some 100,000 kilograms at about $40 per gram.

Several recent studies have predicted that in the next two decades, sales in biotechnology products in human health care and agriculture will total between $10 and 15 billion in the United States, and possibly as much as $30 billion worldwide.
THE LICENSING PROCESS FOR BIOLOGICS

APHIS assesses risks through its application review process. I wish to review some of the steps and point out the safeguards that have been built into the system.

A US Veterinary Biological Product License is required for each product produced in a licensed establishment. All products are evaluated individually to determine the necessary testing for purity, safety, potency and efficacy.

In regard to information, APHIS published its policy for protecting certain privileged or confidential business information in the Federal Register of 23 September 1985 (2). This policy applies not only to veterinary proprietary information, but also to confidential information in any APHIS program. Our policy is that documents which meet the Freedom of Information Act exemption for confidential or privileged information containing trade secrets or commercial or financial information, will be protected from disclosure. All such information is physically secured, and we notify firms of any requests from non-Federal sources. Further, unauthorized disclosure of such information by Departmental employees is prohibited by the Trade Secrets Act.

Categories of products licensed

For the purposes of licensing, biologics derived by genetic engineering may be classified into three broad categories, based on their biological characteristics and safety (Table I).

TABLE I

Categories of biologics derived from biotechnological processes

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Inactivated recombinant DNA-derived vaccines, bacterins; bacterin-toxoids, virus subunits, or bacterial subunits.</td>
</tr>
<tr>
<td>II. Live micro-organisms modified by adding or deleting one or more genes.</td>
</tr>
<tr>
<td>III. Live vectors carrying recombinant-derived foreign genes that code for immunizing antigens or other immune stimulants.</td>
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</tbody>
</table>

The first category includes inactivated rDNA-derived vaccines, bacterins, bacterin-toxoids, virus subunits or bacterial subunits. These products pose no risk to the environment and present no new or unusual safety concerns. Monoclonal antibody products – whether used prophylactically, therapeutically, or as components of diagnostic kits – are also included in this category.

The second category includes products containing live micro-organisms which have been modified by the addition or deletion of one or more genes. Deleted genes may code for virulence, oncogenicity, enzyme activity or other biochemical functions. Added genes may result in the expression of new immunizing antigens or the production of novel biochemical by-products such as beta-galactosidase. It is important that genes added or deleted do not compromise the safety characteristics
of the organisms. In most cases it is expected that they will be improved and would therefore not pose any new threat to humans, other animal species, or to the environment.

The third category includes products using live vectors to carry recombinant-derived foreign genes that code for immunizing antigens and/or other immune stimulants. Live vectors may carry multiple recombinant-derived foreign genes since they can carry large quantities of new genetic information. They are also efficient for infecting and immunizing target animal species. These properties make vaccinia virus recombinants very popular candidates for vaccine development programs.

In addition to vaccinia, other vectors currently being evaluated by licensees, applicants, and other research organizations include bovine papilloma virus, adenoviruses, herpesviruses, baculoviruses and yeast.

Licensing procedures

The general requirements for licensing products are summarized in Table II. Products using modern biotechnological procedures, such as rDNA, chemical

<table>
<thead>
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<th>TABLE II</th>
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<tr>
<td>General licensing requirements</td>
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</table>

| Preparation and certification of master seed (bacteria or virus) stocks |
|↓|
| Manufacture of experimental product to minimum outline specifications |
|↓|
| Host animal efficacy (immunization and challenge) |
|↓|
| Development of potency test for serial release |
|↓|
| Preparation of three consistency serials |
|↓|
| Field safety tests |
|↓|
| Satisfactory completion of all test requirements in “Outline of Production” |
|↓|
| Submission of samples to National Veterinary Services Laboratories for confirmatory testing |
|↓|
| Licensing |
|↓|
| Accept labels |
|↓|
| Release of prelicensing serials |
synthesis, or hybridoma technology, are treated similarly to products prepared by conventional techniques. Special assays may be required for potency and stability determinations, and additional tests may be required to assure safety, especially when live micro-organisms are present (3).

If an application is sent to us for a certain class of product for which a body of data already exists, such as monoclonal antibodies or hybridomas, the review process will be considerably shorter. For example, in the case of monoclonal antibodies, the specificity and potency of these products will be compared with — and must be at least equal to — that of similar polyclonal antibody products.

To assist in maintaining uniformity of production, licensees are required to derive seed materials for production from a lot of seed material which is defined as the Master Seed. Master Seeds of micro-organisms at specific passage levels are selected, identified, and permanently stored by the licensee. Master Seed and final product are tested to assure purity, safety, identity and immunogenicity.

The Master Seed for rDNA-derived products will consist of a plasmid or virus carrying the inserted gene. The constructed plasmid is then introduced into the appropriate eukaryotic or prokaryotic expression system selected for vaccine production. Genomic DNA may also be transferred directly into a variety of mammalian cells. Alternatively, in such cases, the stable transfected cell will be considered as the Master Seed (Table III).

### Table III

**USDA licensing policy.**

**Proposed Master Seed for rDNA-derived products**

<table>
<thead>
<tr>
<th>Constructed plasmid</th>
<th>Expression system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eukaryotic</td>
<td>Prokaryotic</td>
</tr>
<tr>
<td>Transformed cell</td>
<td>E. coli</td>
</tr>
<tr>
<td>Transfected cell</td>
<td>B. subtilis</td>
</tr>
<tr>
<td>Scale up</td>
<td>Production and</td>
</tr>
<tr>
<td></td>
<td>Recovery</td>
</tr>
<tr>
<td></td>
<td>Final product</td>
</tr>
<tr>
<td></td>
<td>(Master Seed x + y)</td>
</tr>
</tbody>
</table>

Recombinant DNA Master Seeds will be characterized by providing a construction map of the bacterial plasmid containing the new gene. Background information concerning the rDNA procedures used to isolate, purify and identify genetic material from one source and the modification used for the insertion of this material into a
new host is required. Data from cloning isolation, proliferation and selection of genetically unique cells would be retained by licensed applicants. The manufacturer must provide a nucleotide sequence analysis in order to characterize adequately the foreign DNA used to code for a particular antigen (Table IV).

**TABLE IV**

**Proposed characterization of rDNA Master Seed**

<table>
<thead>
<tr>
<th>Constructed plasmid</th>
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</thead>
<tbody>
<tr>
<td>1. Nucleotide sequence</td>
</tr>
<tr>
<td>2. Polyacrylamide gel analysis</td>
</tr>
<tr>
<td>3. Drug resistance</td>
</tr>
<tr>
<td>4. Restriction enzyme mapping</td>
</tr>
<tr>
<td>5. Description and location of initiators and promoters</td>
</tr>
</tbody>
</table>

Ingredients of animal origin used in production must meet accepted standards of purity and quality.

Primary cells and cell lines used for production of a Master Seed or vaccine must be in accordance with USDA regulations. All cell substrates must be shown to be free of bacteria, fungi, mycoplasmas, viruses and other extraneous agents. Cell lines need to be characterized and karyotyped for genetic stability. Tumorogenicity and oncogenicity tests must be conducted if there is evidence that the cell may induce malignancies.

Immunogenicity of vaccines must be supported by statistically valid host animal immunization and challenge studies.

The manufacturer must select “Outlines of Production” that include procedures to ensure consistency and recovery of specific antigenic material. Recovery procedures must include removal of excessive antibiotic levels and undesirable fermentation by-products such as excessive bacterial endotoxins. Some in-process test procedures which might be used for monitoring purposes are presented in Table V.

**TABLE V**

**In-process test monitoring procedures**

| 1. Growth rate |
| 2. SDS gel mapping |
| 3. Antibiotic resistance |
| 4. Metabolic markers |
| 5. Molecular weight |
| 6. Activity |
| 7. Percent protein |
Serial release tests in the final product testing of rDNA products for purity, safety and potency will be required. In addition to these tests, product characterization will be required to demonstrate gene expression. Examples are listed in Table VI.

**Table VI**

*Final product evaluation*

1. Purity — standard procedures applicable
2. Potency — correlation of efficacy testing with *in vivo* or *in vitro* procedure
3. Efficacy — standard host animal immunization and challenge data
4. Safety — anticipate expanded laboratory and field testing programs
5. Gene expression — partial sequence analysis
   - high performance liquid chromatography
   - peptide mapping
   - polyacrylamide gel analysis
   - molecular weight determination

To date, APHIS has licensed 19 products manufactured from biotechnological processes. Eighteen belonging to category I are outlined in Table VII. The first, a bacterin, was licensed on 5 October 1983.

**Table VII**

*Licensed products derived from biotechnological processes*

<table>
<thead>
<tr>
<th>Product class</th>
<th>Number</th>
</tr>
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<tbody>
<tr>
<td><strong>Category I</strong></td>
<td></td>
</tr>
<tr>
<td>Bacterin</td>
<td>5</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>2</td>
</tr>
<tr>
<td>Diagnostic kits</td>
<td>11</td>
</tr>
<tr>
<td><strong>Category II</strong></td>
<td></td>
</tr>
<tr>
<td>Vaccine</td>
<td>1</td>
</tr>
</tbody>
</table>

In January 1986, we licensed the first category II product, a modified live-virus vaccine developed through genetic engineering. More than 750,000 doses of this gene-deleted pseudorabies vaccine have been produced and distributed. Shortly after the product was licensed, opponents of genetic engineering sued the Department, asserting that the safety of the vaccine was not determined. However, no safety problems have been linked to any genetically-engineered products licensed by APHIS.
The gene-deleted pseudorabies vaccine is a good example to show the necessity for the APHIS requirement that license applicants generate the necessary safety data. At present, a legal dispute exists between the genetic engineering research firm that was granted the patent for the process and the corporation that produced and marketed the vaccine. One issue involves the credibility of the safety data submitted to the vaccine manufacturer by the patent holder. However, the manufacturer was required to generate the safety data relied upon by APHIS prior to issuing the license, and this data was verified by the APHIS laboratory at Ames, Iowa.

Earlier this year, APHIS granted approval for limited field trials to test a second genetically-engineered pseudorabies vaccine. The vaccine trials will be conducted in swine in six of the major hog-raising states.

THE DEVELOPMENT OF GENE PROBES AS DIAGNOSTIC TOOLS

DNA hybridization is another technique which was once confined to research laboratories and has now become part of a simple *in vitro* test. The two strands of the genetic material DNA will hybridize with each other even in the presence of a large number of other non-complementary molecules of DNA. This technique forms the basis of a very sensitive means for detecting and identifying a variety of infectious agents.

While probes exist for a wide variety of agents and gene sequences, they were initially developed to aid investigation of the basic molecular biology of organisms. In recent times, however, the technique has shown great promise in producing diagnostic reagents. There is a subset of diagnostic applications for which DNA probes are uniquely suited.

Their foremost application, and one for which there is little competition from biochemical or immunochemical tests, is in epidemiological investigations where material is collected in field studies and either tested immediately or saved for screening at a later time. One recent example is tracing for drug-resistant *Salmonella newport* infections in animals fed antimicrobials (4). Another application to which DNA probes are uniquely suited is the detection of micro-organisms, such as mycoplasmas or leptospiroae, which grow poorly or not at all on laboratory media, and which show a wide antigenic variation (5).

The extraordinary promise that DNA probes have shown for the diagnosis of infectious diseases has not yet been fully realized. The principal reason for this delay is the rapid development of fast and sensitive immunoassays, most of them based on monoclonal antibodies. Other factors limiting their full implementation as diagnostic aids involve the development of suitable procedures for sample preparation and a high specific-activity, non-radioactive DNA tagging procedure.

With the advent of new high technology processes such as hybridomas producing monoclonal antibodies and DNA hybridization, new diagnostic reagents are already available for a variety of diseases of animals, including poultry. New diagnostic kits must be carefully evaluated and compared to standard methods to ensure that the new kits clearly demonstrate sensitivity, specificity and reproducibility that is equal to or better than standard methods.
The diagnostic tests used in veterinary medicine and derived from biotechnological processes vary in complexity from highly sophisticated tests using automatic equipment to simple “dipstick” tests for use in the field. More and more, however, the trend is towards simple-to-use kits which combine specificity and sensitivity with speed and economy. Although the principles and technology involved in the development of these tests may be highly sophisticated, they can be used by people without specialized training or equipment.

Regardless of which diagnostic procedure is chosen by veterinary clinicians or selected and recognized as “official tests” by animal health officials, valid results will be obtained only if certain criteria are met:

- the test chosen is appropriate for the particular circumstance;
- the quality of the sample used for testing is ensured;
- the sample is collected at the optimum time and is transported and/or stored under proper conditions;
- there is a thorough understanding of the factors likely to interfere with the results;
- the sensitivity, specificity, and principle of the test are understood;
- the operator is sufficiently skilled to conduct the test and, when necessary, interpret the results.

The dipstick tests for field or on-farm use by the veterinarian or farmer offer great appeal. However, it must be remembered that the limitations and restrictions on such tests are much greater than on tests designed for use in the laboratory or clinic. Such tests must not only be simple to perform; they must produce reproducible results under a wide variety of environmental conditions which may be encountered in the field. For example, they should give valid results over a wide range of ambient temperatures. The end-point must be clear and easy to read.

A special challenge in the use of diagnostic kits relates to the control of their field use. Most of the tests are easily conducted and amenable to use by practicing veterinarians, farmers and ranchers. Except for those diseases which are subject to present or future official control programs, there may be relatively little or no control placed on the distribution and use of kits.

It can be assumed that field tests will either be marketed directly to the farmer or rancher, or via the veterinarian. There is concern that misleading results may be obtained by a layperson if the specific background and principles behind a test are not fully explained. While the use of the kit may be simple, the interpretation of the results will not be. There is a danger that kits which may not fulfill the requirements and expectations of the end user may bias the market against developing improved products which may become available in the near future. Therefore, a clear description of the use of the new in vitro diagnostic test along with the kit’s limitations is very important. A kit designed for one type of application will very likely be unsuitable for a different use without modification.

As the trend to intensified farming and ranching continues, herd sizes will increase. As herd sizes increase, so will population densities. Rapid and accurate disease diagnosis therefore becomes more important. New diagnostic reagents will be needed to detect sexually-transmitted diseases, production-oriented diseases, and diseases that
limit the export of animals. It is paradoxical that we as regulators of diagnostic reagents will also be benefactors of the new tests: their increased sensitivity and specificity will increase the precision of our regulatory decisions.

As the new and improved diagnostic tests become available, another challenge presents itself not only to the regulator but also to the producers of diagnostic reagents. That challenge is to run assessments on the savings in production costs experienced by producers thanks to products derived from the new technologies. The studies must extend beyond the traditional documentation of disease loss and resultant cost savings, to include such intangible but significant aspects as increased management efficiency and direct savings because of rapid and definitive diagnoses which obviate the need for protracted quarantine measures.

The development of diagnostic reagents with improved sensitivity which can be used to rapidly verify disease problems, both domestic and exotic, is always appealing to state and Federal animal health officials. Monoclonal antibodies and DNA probes continue to dominate our interest. Tools and products of the new biotechnology will have direct application and benefits to APHIS. We are especially interested but also concerned by production of farm test kits. These kits have great appeal but at the same time are worrying because of the profound consequences which their misuse could have. The Government, the biologics industry, and the livestock industry groups must take the lead and inform the public of the dire consequences that would undoubtedly result from misuse. However, the possibility of misuse should not thwart the development of the new technology.

In summary, we as regulators are faced with a delicate situation. As the techniques of the new biotechnology advance, there is the potential for tremendous improvements which would overcome many of our pressing problems in animal health. Therefore, we are eager to accelerate the process to obtain them. As stated previously, our goal is to foster a regulatory climate that encourages the innovation, development, and commercialization of beneficial new products derived from biotechnology, while implementing a responsible regulatory policy that limits potential or real risks. We as regulators must recognize that these products must not only be safe and efficacious, but also engender public confidence in their safety. This at times delays and may even hinder the development of products. We must strike a balance in evaluating the safety and efficacy of the products in the shortest time possible while not eroding public confidence in our regulatory policy.

We believe we have the procedures and expertise to meet the challenge. To dispel the harmful myths that can unnecessarily delay our realization of the potential of biotechnology requires support from the whole scientific community.

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RÉGLEMENTATIONS RELATIVES AUX PRODUITS A USAGE VÉTÉRINAIRE PRÉPARÉS PAR LES MÉTHODES BIOTECHNOLOGIQUES, ET UTILISATION DE CES PRODUITS. — J.W. Glosser.

Résumé : L'auteur présente la législation en vigueur aux Etats-Unis et le rôle du Service d'inspection sanitaire animale et végétale (APHIS) dans l'homologation des vaccins et des produits de diagnostic préparés par les méthodes
biotechnologiques. L'emploi des réactifs destinés aux épreuves rapides de diagnostic apparaît très prometteur, bien que des précautions soient à prendre pour éviter une mauvaise utilisation de ces produits.

MOTS-CLÉS : Biotechnologie - Diagnostic rapide - Etats-Unis d'Amérique - Homologation - Législation - Produits biologiques - Vaccins.

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REFERENCES