

*SYMPOSIUM REPORT**Biotechnology Law***table of Contents**

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INTRODUCTION

On November 8 and 9, 1990, the American Law Institute-American Bar Association Committee on Continuing Education presented a symposium on Biotechnology Law which was cosponsored by California Continuing Education of the Bar. The following are short

summaries of the speeches presented at that conference.

Biotech 91: A Changing Environment

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Biotechnology began in the 1970s as an industry dominated by geographic areas noted for their academic resources and populated by academics, rather than business people. Today, there are approximately 1100 biotechnology companies in the United States, one third of which are located in the San Francisco Bay Area. While most companies have fewer than fifty employees, a few companies dominate the industry. The largest nine percent of biotechnology companies employ 55% of those working in the industry and generate almost all of the sales revenue.

With the decline of ready capital from initial public offerings, strategic alliances have become an important source of financing. Bringing even a single pharmaceutical product to market requires approximately \$200 million, thus precluding independent projects by small and mid-sized companies. Strategic alliances with foreign companies can provide access to both capital and foreign markets.

Uncertainty in the FDA's regulatory approval process has also hurt the entire industry and presents substantial problems for marketing products in the United States. The FDA has moved toward using outside panels for advice which often become sidetracked from the main issues of safety and efficacy.

In addition, the backlog on patent litigation has led to a decreased focus on patent protection. Instead, cross-licensing is fast becoming an increasingly popular mechanism for protecting products and settling disputes.

Finally, although regulatory hurdles are increasing for health-care related products and the capital market for new companies is fairly weak, the industry remains reasonably healthy, generating about \$100 billion by the end of the century. The new reality for biotechnology consists of increasing consolidation, efforts at regulatory approval and reimbursements, and changes in government policy.

Product Liability Considerations

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In *Brown v. Superior Court*, the California Supreme Court held that strict liability does not apply to manufacturers of consumer drugs. In reaching its decision, the court looked to comment K of the Restatement of Torts which applies a negligence standard to products that are unavoidably unsafe. The court rejected a case-by-case approach and instead articulated a blanket rule that prescription drugs are not subject to strict liability for design defects.

The *Brown* negligence rule has not gained whole-hearted acceptance around the country. Some courts have explicitly rejected *Brown*, while others have made compliance with FDA regulations a defense only against punitive damages.

While strict liability provided an efficient mechanism for compensating accident victims whereby companies internalized the cost of such social insurance, changing market conditions have made strict liability unworkable. Given the high costs of insurance, strict

liability could stifle important research. Comment K attempts to address this problem by applying a negligence-only standard to products that are essential for human health and need to reach the commercial market quickly.

The core problem behind the strict product liability debate is the cost of medical innovation. The courts should draw from other disciplines, such as antitrust, where difficult issues have been resolved to allow for significant invention. In addition, the courts must distinguish between the negligence and insurance aspects of the law. The twin goals of deterrence and compensation must be kept distinct. Finally, the rules must be designed to maximize human life and health. Therefore, the Restatement should be amended in §402a to read "products for human life or health are presumptively not dangerous without proof of negligence." Compliance with regulatory guidelines should provide a liberal defense, and punitive damages should be awarded cautiously. Judges should also be bolder in finding that there is insufficient evidence to send the case to a jury.

Third Party Reimbursement for Goods and Services

Mr. Wayne Roe

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Biotechnology companies must focus on payment planning as much as seven years before marketing their product. This consideration is especially important if the product involves high clinical visibility, high unit costs, an institutional setting, injection or infusion of the drug, or significant payer market exposure. For most products, insurance companies will pay the lion's share of the costs. However, the presence of any of these factors should trigger an initial evaluation of third party payment.

Previously, insurers paid for any drug with FDA approval. Today, the situation is less clear. To avoid diminishing market penetration, biotechnology companies must be more aggressive. Since the insurance company is the target market, companies must segment the payer market, using information from sources such as the National Hospital Discharge survey.

An example would be a drug that had two possible applications, one for breast cancer and one for prostate cancer. The company would need to consider different patient groups. Breast cancer victims would largely be insured through groups like Blue Cross, while prostate cancer victims are more likely to be on Medicare, which will not reimburse for self-administered drugs. Thus, dosage and method of administration can both have implications for payment.

Patent Strategy for Biotechnology Products

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The term "patent policy" is often associated with the selection of foreign countries in which to file counterpart applications to a patent application originally filed in the United States. However, when properly understood, the subject is far broader, encompassing a number of considerations. These include: (1) obtaining patent protection, (2) exploiting issued patents, (3) enforcing patents, and (4) selecting products based on patent considerations.

Obtaining Patent Protection:

Should an inventor seek patent protection at all? In most cases, the answer is yes, although several situations can militate against patent protection and in favor of trade secret protection. For example, patents for manufacturing processes are difficult to enforce because the process may be practiced behind closed doors where infringement cannot be readily detected. Some inventions are likely to become obsolete well before the patent term expires due to the rapid evolution of the particular technology. In some countries, local law may require mandatory licensing of patents for certain kinds of inventions or may not provide meaningful protection of patents.

There are two schools of thought as to when a biotechnology patent application should be filed. The first counsels the inventor to file early and often in order to obtain the earliest possible filing dates, even at the expense of narrow claims. The second maintains that it is better to defer filing until the best data is available to support the strongest and broadest claims.

Exploitation:

Patents are exploited by means of manufacture and sale of covered products, through licensing transactions, joint ventures, and a variety of other techniques. The selection of the right technique for a particular situation involves the consideration of several factors, including the resources of the patent holder to fully develop and commercialize the invention, the breadth of the patent, and the size and location of potential markets. The feasibility of using patent litigation to prevent others from practicing the patented invention is also an important consideration in this decision.

Enforcement:

The formation in the early 1980s of the Court of Appeals for the Federal Circuit, to which all appeals of patent decisions must now go, has increased the likelihood that patents will be upheld. Despite this, the size of the market for biotechnological products has led large, well-established companies to bring declaratory judgment actions challenging patents issued to small, new biotechnology companies. Patent litigation is very expensive and can consume significant personnel time. For this reason, biotechnology companies must be careful in deciding whether to take an aggressive posture with respect to their patents, lest they attract this kind of litigation.

Product Selection:

The likelihood that a patent will actually issue, the enforceability of that patent, as well as the size and location of important markets each play a role in deciding whether to pursue a particular biotechnology product opportunity. Often these decisions must be made with insufficient information about whether other necessary technology can be developed, whether competing inventors will obtain superior patent coverage, or whether the products for which regulatory approvals are ultimately obtained will correspond to the patents which eventually issue.

Releases to the Environment

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The National Wildlife Federation has a special biotechnology division which is concerned with possible dangers presented by emerging technologies, particularly those presented by synthetic chemicals.

In the past, scientists had always been limited to engineering traits that could be modified through breeding. Now, biotechnology has become extremely powerful, enabling scientists to take genes and transfer them across taxonomic barriers.

So far, there have been over 100 approved releases of genetically engineered organisms in the United States, including transgenic plants such as alfalfa, corn, cantaloupe, and walnut trees. Certain microbes such as *Rhizobium* have also been field-tested.

The main players are large chemical companies and, to a lesser extent, universities. From the perspective of the National Wildlife Federation, there are three types of risks. The first is a direct risk that the organism released into the environment will have a harmful effect. Fish that have been engineered to be more tolerant of colder waters might be a good example. These newly tolerant fish might inhabit waters not previously available to them, thus displacing the original inhabitants and upsetting the ecosystem. A similar problem might result from putting pest-tolerant genes into plants that have nearby relatives that are themselves weeds. The resistant gene might be transferred to the relative, creating a more invasive weed that would be difficult to control.

Secondary effects can also create problems. Crops designed for herbicide resistance may have an effect on patterns of herbicide use. Increasing the use of herbicides may have serious collateral consequences.

Finally, there are serious ethical risks as in the use of technology to create pollution-resistant organisms. Even if such organisms are made completely safe, it is arguable that resources should not be expended to adapt organisms to polluted areas and instead devoted to eliminating the pollution itself.

Who will pay for releases to the environment that cause damage must also be determined. Liability insurance is currently unavailable for such damage. Moreover, many releases will likely be made by smaller companies who will not have the resources to pay for the damage they cause.

Assigning damages will be complicated by the difficulty in tracing a particular problem to a particular corporation. One solution might be to require molecular signatures on individual genes to allow source identification.

The case of Tryptophan, which is the first candidate for a biotechnology products liability suit, may address these issues. Tryptophan is a common, naturally occurring amino acid. Preparations of this amino acid made by one company caused 27 deaths. While the reasons for the disaster are unclear, there is a disturbing implication that genetic engineering may have caused otherwise pure preparations to become lethal. Given the potential for this kind of damage, the government must take a leadership position to safeguard the technology, the industry, and the public health.

Ownership of Biological Materials (The Moore Case)

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John Moore v. Regents of the University of California, 51 Cal. 3d 120 (1990):

In August 1976, John Moore came to the U.C.L.A. Medical Center with a rare form of leukemia. His spleen was removed as part of the treatment, and he returned for follow-up visits from October 1976 to September 1983. The doctor treating Moore requested that his research assistant obtain a tissue sample from the spleen before it was destroyed in order to culture a cell line. At that time, the first of three discoveries was made. While it had been thought that this particular type of leukemia only infected B-cells, it was found that Moore's T-cells were infected. The cell line was then found to produce larger than usual quantities of lymphokines-small proteins that trigger certain immune system reactions. Finally, the researchers discovered that the cell line was infected by a retrovirus, HTLV-2. At that time, only three such viruses were known; namely, the AIDS virus, a virus that caused another form of leukemia, and Moore's virus. In April 1983, the University asked Moore for permission to draw blood for further research.

In August 1979, the University filed a patent application on the cell line, as required by statute to maintain federal funding. In September 1984, Moore filed suit against the University alleging conversion of property and failure to obtain informed consent. Moore sought monetary damages and a declaratory judgment of his rights in the results of the research. While the trial court dismissed the conversion claim on the theory that a person does not have a property right in removed tissue, the appellate court reversed. Since conversion is a strict liability tort, this appellate ruling would have had a broad impact on university research since researchers would be responsible for investigating the source of the tissue and obtaining consent for their research.

However, the California Supreme Court reversed the appellate court decision and held that no property interest exists in excised tissue. In the absence of common law or statutory support, the court concluded that a conversion claim should not be allowed in view of society's interest in the advancement of science, the exposure of third parties to the "lottery of litigation" due to the strict liability aspects of conversion, and the adequate protection provided by the requirement of informed consent. The Supreme Court left Mr. Moore with a remedy, however, because it noted that the requirement of informed consent is not met unless the physician discloses all research and financial interests in the patient's tissue while discussing the patient's treatment options. The extent of Mr. Moore's potential damages for the University's failure to obtain informed consent remains unclear.

Implications of the Human Genome Project

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The Human Genome Project is a research effort being undertaken by the Department of Energy, National Institute of Health, and the Howard Hughes Institute, each of whom are funding their own initiatives. The program at NIH, headed by Dr. James Watson, is aimed at mapping all the human chromosomes at different levels of resolution by different dates. From the perspective of a lawyer, three major problems appear with the project; namely, the creepiness problem, the prediction problem, and the creation problem.

The creepiness problem involves the perception that there are certain types of knowledge that mankind should not have. This concern implies that research projects should have scientific and moral justifications as well as novelty value. In addition, researchers must be open about their procedures and findings. Nonetheless, the creepiness problem is not of paramount importance; such concerns were overcome in the context of heart transplants some years ago.

The prediction problem is more serious, however. As knowledge of the genetic code increases, it will be possible to tell someone that they will die in a certain number of years from a genetic disorder, such as Huntington's Chorea, even though they have not yet had any symptoms of the disease. This prediction ability raises additional issues for insurers and health care finance in general. In the case of individually underwritten insurance, insurance companies may deny coverage to those who test positive for a genetic disorder. Even if insurers are forbidden from considering the genetic information, anyone who discovers they have the disease will rush to get insurance coverage, which will dramatically raise the cost of insurance for everyone. For employer-provided insurance, employers will have an incentive to discriminate against those likely to become ill. Beyond the cost of enforcement, anti-discrimination legislation may be insufficient because it tends towards overinclusion in some areas and underinclusion in others. Moreover, such legislation may simply encourage employers to stop health-care coverage altogether. National health insurance, however, could provide some answers to the insurance aspects of the prediction problem.

Finally, the creation problem raises several ethical concerns regarding the ability to select genetically superior and inferior individuals. The risk of an explicit government mandated eugenics program seems small since it is unlikely to win political support and it is almost certainly unconstitutional under *Skinner v. Oklahoma*. However, a more insidious problem is presented by denying medical coverage to children born with certain screenable defects, thus creating a *de facto* genetic selection process. In theory, this implicit eugenics program should be relatively easy to eliminate through regulation. Finally, additional ethical problems are created by parents who might want to use this technology to select a child who not only lacks genetic disorders but also possess certain positive characteristics.

Transgenics: Monsters, Madness, or Money? Technical and Ethical Issues Surrounding Animal Biotechnology

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Three types of issues are associated with the genetic manipulation of animals through "genetic engineering."

Patent issues

While it is clear that laboratory animals can be patented (the "Harvard mouse"), agricultural livestock have not yet been patented, and issues related to offspring and royalty payments have not yet been clarified.

Ethical issues

Criticisms of genetically-altered animals, especially those with foreign genes, are based on the notion of unnatural species-tampering, "playing God," and concerns over ecological effects of accidental or intentional release into the environment. In addition, some animal welfare rights activists have argued that such alterations are inherently cruel. However, the Office of Technology Assessment has not

found these to be compelling arguments.

Scientific issues

Transgenic sheep, goats, mice, fish, and other vertebrate animals have been created, and other species will soon follow. The current alteration technique is still inefficient because only a few animals in each cohort actually incorporate and express the new genes, but rapid improvements can be expected soon.

Selection and Use of Experts

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Expert witnesses in biotechnology product liability cases must be selected and utilized with great care and precision. In-house experts can prove invaluable by providing reliable assistance and education to the attorney. This is within the potential protection of the attorney-client privilege. In-house experts can also help select and prepare testifying witnesses. Consulting experts can provide a more detached and objective source of information, though protection of their reports from discovery poses a problem. Nevertheless, the testifying expert is indispensable to introduce supporting materials and objectively discuss the ultimate issues. Moreover, testifying experts can introduce favorable material at trial which is ordinarily inadmissible as hearsay. Thus, a testifying expert can introduce data, literature, and even opinions of other experts provided they form a basis of the testifying expert's opinion.

In biotechnology cases, counsel may best employ experts in the applicable scientific or medical fields, such as epidemiology, product regulation, warning communications, and damages. However, counsel must temper selection of testifying experts with consideration of their qualifications and the potential for impeachment. In general, counsel should consider the expert's credentials, specific experience with the subject matter at issue, availability, location, appearance, ability to communicate, and any prior testimony or writings.

Trier of Fact: Jury vs. Judge

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A trial lawyer's presentation is directed to either a judge or a jury. Of these two, the judge is sophisticated, will read the materials, and will remain attentive throughout the trial. The jury is twelve unknown people whose response to the same case is highly variable. Therefore, the trial lawyer's presentation must be responsive to whether the audience is a judge or a jury.

A judge may communicate to the lawyer whenever he does not understand, but a jury must usually remain silent. If the jurors become confused, they will lose interest. The judge has no such luxury. Thus, the lawyer usually prefers that a judge try the case. However, in patent trials, decision by jury is the rule rather than the exception.

Time, or the lack of it, is the foremost factor requiring simplification of complex technological issues. In the past, judges have not had time for complex technical issues. A judge will not permit juries to sit for a lengthy period in civil suits involving high technology. Furthermore, judges often split the court's days between high-technology trials and criminal cases. Therefore, time constraints strongly influence trial presentation.

A judge wants to hear the detailed development of a case before arriving at a conclusion and is not easily swayed by audio-visual presentations. However, since the jury has no written documents available to it during trial, the lawyer must make briefs and other important written documents available to the jury by videotape, overhead projections, and charts. These also help to retain the jurors' attention. One effective way for a lawyer to communicate a favorable view point is through a "day-in-the-life-of . . ." re-enactment videotape. Using visual aids, a lawyer can convey to the jury within days or even hours the same point that would have taken weeks to

describe step by step.

Because jurors tend to remember visually, a lawyer can display photos of the witnesses during closing argument so that the jurors can understand the summary of the testimonies in light of their recollection of the witnesses.

In addition to using audio-visual techniques to simplify evidence it is essential to determine what evidence is important. Here, an experienced trial lawyer's instinct should ultimately take precedence over the advice of an outside committee of analysts pouring over polls.

A lawyer must not succumb to the temptation of utilizing every tool available. Jurors inundated with audio-visual effects may become so fascinated with the technical wizardry that they may lose focus of the technical issues presented. Therefore jury presentations should be visual, understandable, and brief.

An essential difference between judge and jury is their knowledge of the law. The judge knows the law and the arguments. The jury only knows the facts but not how they apply to the law until instructions are given after closing arguments. The lawyer must present the facts so as to lead the jury to arrive at a favorable conclusion without them knowing what the law is along the way.

Therefore, a lawyer's trial presentation plan should be considered at the earliest pleading with attention to the issues and their proof at trial. Later decisions should be based on this previously established architecture. Witnesses must be presented in testimonial sequence consistent with the scenario developed in the opening statements.

In response to the inadequate presentation of evidence at high technology trials, a federal commission plans to issue a training manual for judges on technical matters. However, with proper presentation technique, lawyers can more effectively persuade not only the judge but also the jury.

Avoiding Pitfalls in Pharmaceutical Licensing

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In the field of biopharmaceuticals, the enormous risk involved in bringing a new product to market encourages creative commercial and financial arrangements between companies to share both the risks and the rewards. The negotiators of these cooperative deals typically have little experience in bringing a molecular drug to market. Therefore, unaware of the pitfalls common to biopharmaceutical licensing, the negotiators conclude deals that ignore problems which often are resolved through litigation.

Several problems exist in the structuring and implementation of a joint effort to bring a biologic to market. The cause of these problems stems from the fact that the FDA looks at biologics differently than pharmaceutical drugs due to the independent centers which evaluate biologics and drugs. Negotiators usually understand pharmaceuticals, but few are familiar with biologics, resulting in numerous pitfalls when dealing with biologics.

A joint effort typically involves a small start-up company and an established pharmaceutical giant. The start-up wants a small share of the market in order to gain a foothold in the industry. The established pharmaceutical company wants new products with marketing rights while leaving the risks with the developer. Despite this inherent tension, both firms share a common interest in knowing whether the biologics or drug department of the FDA will regulate this particular product. The answer should be obtained before beginning negotiations because this information substantially changes the structure of the deal.

The first question this information raises is: who is going to sell the drug? If the biologics center of FDA regulates, only the license holder can sell, unlike the case with drugs. In order to obtain the market rights by holding the license for the biologic, the licensee must also manufacture the biologic. Thus, the manufacturing rights for biologics are crucial and should not be split or given away easily. Furthermore, biologics in general require the entire manufacturing process from top to bottom to be in control of the license holder. Often, pharmaceutical companies want to participate in manufacturing due to increased efficiency and tax shelters, but this participation may cause enormous problems in obtaining FDA approval of biologics.

A second question is: who will share the risks? Risks are involved in developing the biologic through clinicals and in upscaling the

product to commercial form before the biologic can be validated for licensing. The development house, usually the start-up, should develop the biologic for clinical trials. The FDA considers a biologic to be a different product depending on where it is produced. Therefore, the method of upscaling from clinicals to large-scale production by transferring the manufacturing location from developer to pharmaceutical company may alter FDA approval, although this would not happen with drugs. A change in FDA approval would delay the time in getting the product to market as well as increase the costs.

In clinical development, who is responsible? What is the standard of effort required? In this industry, time is money. Suppose manufacturing and marketing were divided separately between the start-up and established company, respectively. Marketing always wants to get the product out quickly, so it insists on the right to control the clinical trial. Who bears product liability for off-label promotion if the marketer chooses a narrow usage on the label to get the product out without performing clinicals on off-label uses?

After clinical trials, who is responsible for obtaining FDA approval? What is the standard of effort? What if the opportunity is fumbled away in that party's hands?

After FDA approval, who has the responsibility of bringing the biologic onto the market? How is this affected by the splitting of rights? What if the start-up depends on the biologic for its livelihood, but the large company decides that this product is now low priority, five years into the deal?

In all of these cases, the parties need to determine who has responsibility, what it is, how to measure it, and what to do if one party is dissatisfied with it. When one party inevitably becomes dissatisfied with the other party, should their dispute be settled by mediation, arbitration, or litigation?

Currently, alternative dispute resolution is popular in corporate America. Unfortunately, no well-developed, routinized, highly defined course of dealing exists in this area. Thus, every contract where an alternative dispute resolution mechanism arises provides an opportunity for new litigation because every single contract is subject to challenge and must be interpreted.

Therefore, alternative dispute resolution techniques must be approached with caution. For example, even if an arbitration clause is included in a contract, California courts retain jurisdiction and can enter interlocutory injunctive relief pending arbitration, notwithstanding the jurisdiction of the arbitrators. Certain federal circuits agree. The Third circuit, for example, held that notwithstanding the Federal Arbitration Act or express statutes against judicial intervention, the court retains jurisdiction to enter injunctive relief on the merits of the arbitral dispute. Therefore, one can simultaneously litigate and arbitrate the same matter.

Litigation is superior to arbitration when an adversary's purpose is not to enlighten and clarify, but rather to misdirect, especially in complex technological areas alien to the common sense of judge and jurors? Litigation allows a collection of jurors' minds, not just one person, to arrive at a result. Among arbitrators, there exists little patience for rules of procedure, rules of evidence, and the devices established over the past several hundred years to eliminate unsubstantiated, extraneous, and misdirected allegations, smears, and innuendoes which have no place in the proper resolution of a dispute. If one desires an effective and rigid application of the law, litigation provides the best route.

Science in the Courtroom

The Honorable William W. Schwarzer

Director

Federal Judicial Center

Washington, DC

With the advent of high-tech issues in the courtroom, it is important to prepare judges for cases involving science and technology. Judges cannot be sent back to school, but there are ways to teach judges about scientific issues so that justice can be better served in the court system.

The critical issue for the judge is to distinguish between a working hypothesis and a scientific fact. However, this is easier said than done.

Consider the following case. One of the leading aerospace engineers in the field testified that by concentrating on the result of the flip

of a coin, one can cause one side to come up more frequently than the other. His experiments showed that in 750,000 trials, heads came up more often, at a rate which had odds of 1 to 5000 if occurring by chance. Is this fact or a working hypothesis? Is there a scientific basis?

Consider another example. Before the polio virus was discovered, experiments showed that the occurrence of polio increased with the amount of Coca-Cola consumed, both of which increased during the summertime. Is this fact or working hypothesis?

The distinction between fact and working hypothesis is a useful analytical device to help judges focus on technological problems in the courtroom. This distinction also brings up a question to consider: what is the responsibility of the judge?

Traditionally, any expert with minimum qualifications can express an opinion. What to do with the opinion is left to the jury. It is frightening to think of all the complex questions on the frontier of science which go to a jury. The jury, however, is limited to what a reasonable jury would find based on the evidence. The role of the judge, then, is to determine what evidence the jury is allowed to consider.

Many judges abdicate this responsibility when confronted with complex scientific problems. Judges, however, should not let evidence go to the jury unless it is founded on an acceptable scientific basis and on valid scientific methodology properly applied. An expert's qualifications must be relevant to the specific scientific question at issue. In addition, the expert must have relied on material that would have been reasonably relied on by other experts in that field.

How can judges be expected to make such determinations when the amount of scientific knowledge is doubling every five years? Judges rarely study science and therefore become intimidated, allowing the jury to decide scientific questions.

First, judges need to realize their function. Their purpose is to resolve legal disputes within a legal structure using rules of burden of proof, not to decide whether specific scientific propositions are true or false. The basic rule for a judge to administer is that the proponent of a proposition has the burden of proof.

Judges must understand a scientific proposition for it to fit into a legal framework. A judge cannot depend on the adversarial process to determine the truth. Experts and patent lawyers often forget how to communicate with lay people. They do not realize that the most effective tool in high-tech cases is not argument but rather enlightenment. Patent lawyers tend to speak in counterproductive scientific jargon. They should speak in plain English and translate complexity into simple language.

Judges, on their part, must play a more active role. They need to ask questions to make an opinion comprehensible in order for them to apply the distinction between a working hypothesis and scientific fact. The fact that other judges accepted an opinion does not mean that the present judge should do the same. Precedent has little influence in this field because technology changes rapidly and enormously over a short period of time.

In addition, judges must not be afraid to look ignorant. The greatest crime a judge can commit is to fail to ask the elementary questions necessary for the judge to understand the essence of the technological issue. Judges need the courage, self-confidence, and interest to ask hard questions and not take anything for granted. Things are not always as they seem.

Judges must also find out why experts disagree. Different assumptions, approaches or value systems may need to be exposed in order to get at the heart of the matter. A court-appointed expert should not be emphasized because no expert is neutral; each comes in with individual assumptions, approaches and values. Therefore, a court-appointed expert will not suddenly make the case comprehensible. However, the court expert does have the limited role of asking the right questions so as to assist the judge in understanding the matter more fully.

One method to improve understanding is for the judge to hold a tutorial prior to the trial where opposing counsel explain to the judge and jury the basics of the science relevant to the contested issue.

Judges should not assume that science always supplies the answers. In fact, science is the search for answers, not an answer in itself. Judges must fit scientific thinking into the legal framework, where scientific language tends to confuse the legal outcome. The bottom line is that lawyers have an obligation to be helpful to the judge in clarifying the truth, not simply to act as confrontational advocates.

Orphan Drug Perspective

Mr. John McLaughlin, Esquire

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In 1980, Congress received complaints about known therapies that were unavailable in the United States and which had to be imported illegally to be obtained. A subsequent survey of the pharmaceutical industry found that at that time there existed 134 known therapies, most of which were not approved, for small diseased populations.

Why did no company seek FDA approval for these therapies? One reason is that the small size of the patient population combined with the huge costs of obtaining FDA approval made companies unwilling to invest in the therapies. In addition, the small size of the patient population rendered it difficult to obtain enough test patients for the clinical trials required for FDA approval. Furthermore, many of the therapies were difficult to patent because they were either old therapies or simply unpatentable.

In response, Congress enacted the Orphan Drug Act of 1983 which provided four incentives for companies to develop these therapies and to seek FDA approval:

- (1) a hefty tax credit
- (2) written guidance on clinical data provided by the FDA
- (3) market exclusivity
- (4) a modest grant program for non-profit research.

The tax credit turned out to be an ineffective incentive; only \$100,000 per year has been claimed by the entire industry since the inception of the Orphan Drug Act. The second incentive failed because the FDA does not in fact respond to requests for guidance, contrary to the provision of the Act. Market exclusivity is the most important incentive to have arisen from this act.

Companies qualify for market exclusivity if:

- (1) the disease in question afflicts less than 200,000 people in the United States; or
- (2) the disease in question afflicts over 200,000 people in the United States but the company has no reasonable expectation of recovering costs from sales in the United States.

The first part of the test can be satisfied by any information on the disease, demographics, or population, whether published or unpublished. If applying under the first test, the population must be under 200,000 at the time the company seeks designation under the Orphan Drug Act. Later increases in the patient population will not affect eligibility for market exclusivity. In contrast, the hurdle of the second part of the test is so difficult to overcome that no company has yet attempted to satisfy it.

This market exclusivity may be limited by proposed legislation requiring the sponsor to project the size of the population in three years and giving the FDA authorization to remove market exclusivity at any time during the seven years granted. These propositions were vetoed in 1990 but will be the focus of Congressional action in the near future.

Assuming market exclusivity is granted, what does it provide? Market exclusivity allows seven years of patent life protection. During that time, no other company can manufacture or market the same drug for the same application. However a different drug for the same application or the same drug for a different application is allowed. In determining whether two drugs are the same, the FDA, in the example of small molecules, looks at the active chemical structure.

Market exclusivity is not granted if the holder of FDA approval consents to approval of a third party or if the FDA determines that the sponsor cannot provide adequate quantities to the patient population. Neither of these conditions have yet been invoked. In addition, the proposed legislation would have two companies share exclusivity if they simultaneously develop the drug.

In conclusion, the Orphan Drug Act has been remarkably successful, standing as one of the most effective public health policy initiatives in the past several decades. This act resulted in the approval of over 40 orphan drugs and the testing of over 150 more in clinicals. Market exclusivity is the reason for the act's success because exclusivity provides the certainty of patent rights, allowing businesses to make decisions.

Patent Law Perspective

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An important patent issue facing biotechnology companies is whether claims for proteins isolated by recombinant techniques infringe claims for proteins isolated by other methods. In *Scripps Clinic v. Genentech*, the court found that although Scripps isolated a protein by natural techniques, it was entitled to a claim which covered the protein "whether derived through its disclosed process or any other process achieving the same result." Because Genentech's recombinant protein is structurally and functionally the same as the natural versions, Genentech's protein infringes Scripps' patent claim. In *Amgen v. Chugai*, the same result was reached with respect to human EPO.

Under the doctrine of equivalents, the court will find infringement, even in the absence of literal infringement, if the accused product is a "rip-off" of the patented invention. Nonetheless, in *Genentech v. Wellcome*, the court found that minor modifications to a protein which change its nature but preserve the same functions were sufficient to avoid infringing a composition claim. In a dispute over Pituitary Growth Hormone, the appellate court was unwilling to rule whether a claim for a recombinant protein would infringe on a composition claim for a naturally purified protein, when the primary sequences of the two proteins differed.

The courts have ruled that a protein created by recombinant methods infringes on the patent rights of a protein isolated by natural methods. These cases have not been argued on the public policy ground that these results are unfair to biotechnology companies, who have spent more time and money to find, in most cases, the only practical method to make the protein. Instead, the courts have focused on narrow, legal patent arguments regarding interpretation of claims, rather than on the purpose of patents. This result, unfortunately, may have a "chilling effect" throughout the biotechnology industry and retard research.

Technology Transfer Act

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The Japanese use "study teams" to acquire knowledge of state of the art research in the United States simply by inquiring at research sites. This knowledge is then used to narrowly focus Japanese research on developing cutting edge commercial applications.

In contrast, government policies in the United States had historically discouraged the development of commercial technologies funded by the 70 billion federal dollars spent annually on research. The requirement that all results derived therefrom remain in the public domain created a disincentive to private industry to make the large investments necessary to commercialize a breakthrough in basic research. By the late 1970s, the United States Government had licensed only 4% of its 28,000 patents for commercial development.

In 1980, Congress restructured the system, allowing university ownership of the patent rights resulting from federally funded research. Upon licensing, royalties remain with the university and a percentage goes to the individual inventor. Incentive to the researcher or inventor is necessary to compensate for the publish-or-perish pressures for early publication that also destroy the chances for international patents. These changes spawned the biotech industry, first at Stanford University, with the inventions of Boyer and Cohen and later at other major research universities.

Under current law, companies can share research costs with universities and negotiate exclusive rights to patent or field of use licenses. This year, there are 500 such public/private agreements. University run laboratories were added to the system in 1984, and federally owned laboratories followed with the 1986 Federal Technology Transfer Act. In 1989, Congress authorized withholding of some information under the Freedom of Information Act for up to five years.

Universities are balancing their public mission to contribute to the scientific dialogue with their commercial interests under the new technology transfer system. However, concerns that the universities will be "bought out" by the private sector, were raised at the 1990 hearings on researcher conflicts of interest. The financial disclosure guidelines developed at those hearings are problematic for research not involving clinical trials or public health.

Finally, further progress can be made by lowering the remaining legal barriers to federal employees owning software copyrights, and by creating a database for industry that details federal research subjects and their status. The Office of Technology Transfer is moving away from eliminating legal barriers and toward encouraging industry participation in the new system. The new stage may include direct consulting with industry to determine which basic research should be funded.

Patent Harmonization

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Procedural Aspects

Existing patent harmonization at the Bureau of PCT has produced several procedural advantages. For example, foreign patent filing decisions may be deferred for 30 months. While there are obvious reasons for filing a patent application as soon as possible after the "concrete embodiment" stage (filing early insures priority rights and blocks other parties from obtaining claims that may interfere with research), there are also situations where delayed filing may be advantageous under foreign laws. The 30 month deferral provides flexibility in relation to these issues. Another procedural advantage is the low patent-search per year ratio that an examiner performs. Furthermore, the procedures are economical due to credits given by the European Patent Office.

The Rationale for United States Involvement in Harmonization

The United States formerly had the distinction of having the best patent system in the world; however, this is no longer the case. The current international system, derived from a model set of principles for substantive patent law, improves upon the American system. The United States can gain two benefits from harmonization: a grace period, and better protection for claiming in Japan. The benefits that will result from joining harmonization outweigh negative factors, such as a restrictive filing date.

TRIPS

TRIPS (Trade Related Aspects of Intellectual Property) is one of the elements of the Uruguay Round of the GATT. Two elements of TRIPS pertinent to the patent field are minimum standards and the United States' continued involvement in the harmonization process.
