Capitalizing on Wealth in Biotechnology

Effective cooperation between industry, universities, governments will result in significant gains for mankind

BY JOHN H. WOODLEY*

The quest of mankind is simple — to live! This quest can be readily satisfied by an abundant supply of food and quality health care. Biotechnology holds the promise of satisfying this demand.

Biotechnology has been exploited to the benefit of mankind for thousands of years. Some of the earliest and most enjoyable exploits involve the production of wines and beer. Other, no doubt more significant exploits involve improved animal husbandry by selective breeding, improved crop varieties, and more recently the production of penicillin from fungi and the development of viral vaccines.

Why is there now an interest in the transfer of this technology when it has been with us for so many years? The answer is simple. In man's desire to solve the "riddles of life," he discovered in the early 1970s that a living cell's function can be altered significantly in a controlled and reproducible manner. Significant features of the immune response system are now understood and the production of monoclonal antibodies for use in diagnostics is a commercial reality. These recent discoveries have resulted in significant improvements in the production of foods and health care.

The benefits of biotechnology in recent times include the manufacture of: human proteins, such as Interferons; human insulin; human growth hormone; improved production of existing antibiotics such as cephlosporins; and new and effective diagnostic agents based on monoclonal antibody technology. Examples are those used in the early detection of certain types of cancer, viral and bacterial infections and heart disease.

Other areas include improved waste disposal and treatment of effluent from industries and the leaching of minerals from ores, all involving the use of specially developed microorganisms. In agriculture, examples include the development of new strains of grain, new strains of vegetables, nitrogen fixation in corn, frost resistance in vegetable crops, and improvements in livestock management. The potential for these developments in the marketplace is truly unlimited, because they meet man's quest to live by providing food and health care.

Sim & McBurney, Toronto, Ontario, Canada; paper presented at LES/UNIDO meeting, Vienna, Austria, November 1986.

WHERE IS THE TECHNOLOGY DEVELOPED?

Biotechnology is derived from research efforts in four primary centers — universities, industry, joint ventures of industry and/or universities, and research centers sponsored by local or federal governments.

Only two, industry and joint ventures, are in a position to commercialize the fruits of their research. Hence universities and research centers find themselves in predominantly a licensing-out position and industry and joint venture groups find themselves predominantly in a licensing-in position. Industries do, however, enjoy the luxurious position of being able to commercialize what they develop. Industry may decide from time to time to retain an exclusive position sometimes worldwide for the particular area of biotechnology they have developed.

However, this is the exception to the rule. Generally, significant developments in the area of biotechnology are licensed out by any one of the above concerns, either on the basis of entirely developing and commercializing the discovered biotechnology or developing in regions that are not competitive with the commercial interests of the industry that has developed the technology. Therefore, developments in biotechnology have provided a fertile region for technology transfer normally by way of license agreements, which include transfer among groups in a particular community, region or country and also among countries.

HOW IS THE TECHNOLOGY TRANSFERRED?

There is a wide divergence in the manner in which biotechnology is transferred by the various above-noted groups. It is usually in the university's interests to license technology on a nonexclusive basis for one or more territories based on one or more uses of the developed technology. For industry, if it is large, it is normally in its best interest to license the technology in areas that are not competitive with its own exploitation of the technology. For smaller companies, it can sometimes be a vital function of the business to license the technology to gain the necessary large investment to commercialize the product and gain a market position. Witness Genentech with its development of human insulin, which is now marketed by the pharmaceutical giant Eli Lilly.

There is one common consideration for all of these groups when a decision is made to license the technology — a marketing program.

> *"If a man can write a better book, preach a better sermon, or make a better mousetrap than his neigh-*

bors, though he builds his house in the woods, the world will make a beaten path to this door"— Ralph Waldo Emerson

This is wrong! The development must be advertised in order to be exploited. The best form of publicity is scientific publication, either in journals, published patents or patent applications. These venues suit the needs of all of the above entities. Universities and government-sponsored groups survive by publication in journals. Industries normally survive by way of patent protection on their developments.

Other forms of promotion of the technology, of course, include, presentations at technology forums and meetings, advertising in trade journals and personal contact with selected companies which are thought to be interested in the particular development.

Another significant form of advertising of the technology is commercial success. However, this is normally a luxury only enjoyed by industry which has the depth and capabilities to commercialize the developed technology.

PROTECTION OF THE TECHNOLOGY

It is important to decide before any transfer of the technology on the manner in which the technology will be protected. Biotechnology is protectable by utility patents, plant variety patents and trade secrets.

The protection of technology by trade secrets, if closely supervised and controlled, can be the longest form of protection available. However, the control aspects must be rigorously enforced. It is clear that biological inventions are protectable by trade secrets. Such inventions may involve newly discovered or engineered microorganisms, cell lines or their progeny, and newly created strands of DNA embodied in vectors or hosts. It is appreciated, however, that once the technology relating to any one of these embodiments of the biological invention becomes public, protection by way of trade secrets is immediately lost. There are, of course, many steps which can be taken in controlling trade secrets to ensure against their misappropriation and disclosure to the public. For example:

1. Highly secure areas can be developed in research and manufacturing areas.
2. Only certain employees are made aware of the trade secrets and are bound to secrecy by appropriate agreements.
3. All publications by the group that is aware of the trade secrets are reviewed before release to insure that the company's proprietary information is not disclosed.

However, should there be a slip or loss of control and the trade secret becomes public, then trade secret protection is automatically lost. If the trade secret becomes public through misappropriation, fraud or other criminal act, the persons responsible are liable. However, this may result in minimal compensation to the owner of the trade secret.

In the field of biotechnology, the critical information in terms of technical material can be carried in a single microorganism. Since there may be billions of microorganisms in a fermentation system, it is almost impossible for a company to maintain control over what happens to those microorganisms. For example, if a scheme is properly devised, microorganisms could be salvaged from the waste materials of the fermentation process and grown by the unauthorized party to achieve all the benefits of the trade secrets.

A significant drawback with the trade secret approach is that it does not advance the technology in a particular area. Trade secrets automatically exclude publication of important data. This prevents others learning about the technology and improving on same for the benefit of every one.

Protection

The transfer of technology is predicated on protection of such technology. That is, if the party receiving the technology has no competitive advantage over its competitors, then the technology is not worth buying. However, competitive advantage can be obtained by receiving know-how and trade secrets from the owner of the technology and/or the promise of market exclusivity due to patents in the particular country. These principles apply to any technology being transferred, but more so to biotechnology.

In the particular area of biotechnology involving plant propagation, an alternative to trade secrets is protecting plants by way of various plant variety protection patents. There are several countries that offer, in one form or another, a type of plant patent. The Union for the Protection of New Varieties of Plants (UPOV) is an international convention respecting plant protection. Several countries belong to this organization, including Belgium, Denmark, France, West Germany, Israel, Italy, the Netherlands, South Africa, Sweden, Switzerland, the United Kingdom, and the United States. The convention is directed at protecting plants developed by sexual reproduction. This should be compared to the Plant Patent Act of the United States, which is directed at protecting plants reproduced asexually. The Plant Patents Acts in the various countries, therefore, offer an alternative form of protection compared to trade secrets, which enable the licensing of new plant varieties.

Another form of protection is by utility patents. Some countries, such as the United States and Australia, have extended patent protection to cover plants. This results in publication of technology that can be constructive in developing new technology. However, it is appreciated that with patent protection there are many significant drawbacks on the scope and strengths of patent protection available on biological materials. Conformity in the laws protecting biological materials is developing in several European countries. Similarities in the law have also been developed in Canada, the United States, Japan, Australia and New Zealand. However, there are many countries that still do not recognize the patentability of biological materials in any form, including microorganisms or other biological systems.

There are several stumbling blocks on the road to gaining solid patent protection on biological materials. There is the prevailing thought that patents on life are not socially acceptable. This has affected decision-making in many jurisdictions regarding the patentability of biological materials as they exist in various types of life forms ranging from microorganisms to human cells.

Important Consideration

There is one important consideration that is unique to the field of patenting biotechnology. As is generally understood, in order for a patent to be valid it must disclose the invention in terms that will enable those skilled in the art to work the invention when the patent has expired. In biotechnology, there are many developments that may happen by chance mutation, chance isolation of a useful monoclonal antibody, and chance isolation of a valuable piece of DNA to produce a valuable protein or act as a medical probe. Quite often these discoveries cannot be replicated even though the starting materials are known.

The discovery may well be patentable. However, how does the inventor satisfy the sufficiency of disclosure requirement. This hurdle has been overcome by developing procedures in various countries that provide for deposition of the microorganism containing the valuable information in a depositorium recognized by the Budapest Treaty. Providing the deposit is made in accordance with the procedures of the various countries, valid protection can be obtained on the basis that the deposits are freely available to the public after the patents have issued or the applications have been published. Hence the public has access to the invention even though the disclosure may be insufficient in fully describing the characteristics of the life forms, or other types of biological materials to enable replication of the claimed invention.

The key thing often overlooked, however, is that the deposit should usually be made before the patent application is filed. As a general rule, I advocate that deposits of the claimed microorganisms or related material should be arranged and their viability be established in the recognized depositorium before the first patent application is filed. In this manner, all rights of the inventor are preserved and patents for invention can be safely filed in all countries in the world which recognize patents on various forms of biotechnology.

It must be emphasized that strong patent protection in a country leads to improved biotechnology transfer into and out of that country. An example of this position is a paper published by the Canadian Government under the auspices of the Department of Consumer and Corporate Affairs. I believe it reflects at least one country's positive outlook on the benefits of licensing of biotechnology.

HANDLING OF SERIOUS INQUIRIES ABOUT TECHNOLOGY

Presumably, if the technology owner has done a good job in marketing the technology and protecting the technology, there will be inquiries from interested parties about the technology and what is its potential to satisfy mankind's quest.

Normally this involves transfer of information concerning the technology that may include biological materials relating to the technology. Once the owner has established the serious inquiries, initial steps can be taken to transfer information concerning the technology. If the person receiving the technology is in the same country, the proceedings are simpler than if the transfer is to another country. Most countries already have in place government regulations controlling the flow of technology into and out of the country in question. It is therefore imperative to determine before any technology is released that (a) the technology owner has a right to transfer the technology to the foreign group, and (b) the foreign group is in a position to receive and use such technology.

I will not attempt to cover various aspects on export controls and licenses required in gaining government approval concerning technology transfer. In my country, Canada, there are detailed regulations and controls concerning the transfer of technology, much of which is dependent upon the type of technology and the country to which it is being transferred.

LETTER AGREEMENTS

Having determined that the technology can be transferred to another party, either for preliminary investigation or collaborative research pusposes, such transfer has to be protected by way of a confidentiality agreement that is commonly referred to as "Letter Agreement." Depending upon the activity of your research center, several of these letter agreements could be entered into yearly. The agreements provide an effective form of recording transfer of biological materials into and out of your research organization.

It is appreciated that one should be wary of any standardized form of letter agreement. For every exchange there is always a new set of facts. There is, however, a sample "Letter Agreement" by Kelly and Jaworski, "Agreements Covering Exchanges of Biological Materials." When considered with the following detailed issues, most of the critical areas in the transfer of biological materials are covered.

It has to be remembered that, with biological materials an accidental release of just one organism containing the essential information can result in unauthorized use of the invention perhaps without the originator even knowing. Each microorganism containing the essential genetic information must be looked upon as a miniature factory all onto itself — "a turnkey operation."

Hence extreme care must be exercised to maintain confidentiality on the information and materials before biological materials are released to another party. The biological material to be transferred should be sufficiently described to ensure that there is a clear understanding between the parties as to exactly what materials are being investigated. Another consideration is the concern that health regulatories have with regard to improper use of biological materials or inappropriate handling; i.e., biological warfare or release to the environment of a toxic microorganism. In the United States, the National Institute of Health has rigid guidelines covering the development, use, and testing of genetically engineered biological materials. It is important to ensure that the group receiving the biological material agree to use the materials in compliance with all laws and regulations of their country and as a yardstick, reference may be made to the current National Institute of Health guidelines as set down in the United States. Furthermore, the group receiving the biological materials should agree to save and hold harmless the transferor of the material in the event of improper use by the receiving group.

Improvements

Another consideration is that during the research investigations, improvements to the biological material and process may result. It should be appreciated that improvements to the biological material may involve modifications thereto. Therefore, the issue of "derivatives" should be addressed in the "Letter Agreement." It should be clearly understood between the parties that any development that results in deriving functional material from the biological material transferred is encompassed by the agreement and hence the group transferring the biological materials should have rights thereto. The breadth of the derivative definition will depend on the fact situation for the biological transfer. Hence the transferor should reserve at least the right to negotiate a license from the receiving group to practice any patentable improvement or other important information developed by the receiving group during their investigations or research. Such investigations may also involve the development of subject matter that the receiving group wishes to divulge in an abstract or manuscript for publication in a scientific journal. It is important to ensure that the receiving group present all such papers to the transferor before publication to ensure that no valuable information in which the transferor may be interested is released before appropriate steps are taken to protect the information.

LICENSE AGREEMENT

Now that the biological material has been transferred and work is underway to investigate the transferred biological materials, hopefully the investigations will result in a licensing arrangement whereby the licensee desires to obtain all relevant information concerning the transferred materials so as to be in a position to commercialize the development. Although, as already noted, biotechnology has been with us for thousands of years, it is only of late that licensing biotechnology has taken on significance and has required special considerations in drafting license agreements to suit the needs of the licensor and licensee.

There are as many ways to approach drafting a license agreement covering a biotechnology transfer as there are transfers.

However, with the basic issues of licensing in hand, I believe a review of the important principles in a biotechnology transfer will provide sufficient information to deal with situations as they arise. In deciding the strategy of licensing a technology, either in the form of licensing out or licensing in, careful consideration has to be given to: (a) whether it is going to be an exclusive position or nonexclusive position, (b) fields-of-use and territorial restriction, and (c) monetary rewards.

These issues become extremely important in licensing biotechnology because many developments of today might have only one form that is ready for market, yet there is a wide variety of other applications of the technology not yet developed. As a rule of thumb in the development of a "pioneer" biotechnology discovery, the licensing posture should be on the basis of a nonexclusive license with a field-of-use restriction and in a particular territory. In opposition to that, with a biotechnology that has been developed and has very specific application, an exclusive license posture should be favored without any field-of-use restrictions and optionally with territorial restrictions.

How these basic aspects are brought together in a licensing program also depends on the source of the technology, whether it be from industry, universities, collaborative research or joint venture. Universities are in the most vulnerable position because of the ambition of the professors and researchers to publish their findings as developments occur. One normally has to act very quickly in protecting university technology to ensure that a position is maintained which can be licensed to others.

Example

My favorite example of how a university capitalized on a pioneer technology to result in considerable revenues was developed at Stanford University. They were in a position to license the basic Cohen and Boyer technology on recombinant DNA developed jointly at Stanford and UCLA universities. To encourage licensing this technology, a credit system was provided on the minimum yearly royalty of $10,000, providing the nonexclusive license was taken out before a specified date.

Hence, the "early-bird" principle.

After that date, the credit system was removed so that the minimum royalty of $10,000 a year was due every year. Surprisingly, this technique encouraged some 73 groups to take out a nonexclusive license under the Cohen and Boyer patent in the United States before the due date. I understand that the program is now gathering approximately $2 million a year in royalties, which exemplifies a workable approach to licensing basic developments in biotechnology. By comparison, if the patent program is directed to a specific area of the technology and it may only be used by no more than three or four licensees, then the upfront buy-in early scheme will not work. At that point everybody would recognize the advantages of the technology and buy in immediately.

The purpose of a license agreement in the transfer of biological materials is to protect and set out the rights of the licensor and licensee to an agreed to format that contains provisions beneficial to both sides. The licensor is usually in the position of drafting the agreement for consideration and negotiation with the licensee. This is particularly important in the field of biotechnology because of the intimate familiarity the licensor has with technology about to be transferred. The major issues in biotechnology licensing are:

1. Ownership.
1. Derivatives.
3. Type of grant.
4. Field-of-use restriction.
5. Territorial restrictions.
6. Licensing fees and royalties payable.
7. Multiple licensing to exploit the particular technology — royalty layering.
8. Confidentiality with respect to trade secret.
9. Improvements to the licensed biotechnology.
10. Enforcement of licensor's patent rights and de-

fending against third party infringments.
11. Health and environmental approvals.
12. Export approvals for technology.

OWNERSHIP

Biological materials can be derived from a variety of sources. With any licensing program, it is important to establish ownership in the technology being licensed. This is even more critical in biotechnology, because of the diverse origins of same. If one isolates from nature a valuable microorganism for producing an antibiotic, then unquestionably the person who uncovers the valuable microorganism is the owner of that microorganism unless it has been assigned to others. Similarly, one who genetically engineers a new microorganism to produce a new product or an old product is also clearly the owner of that development. However, the issue becomes somewhat cloudy when the biological materials are isolated from biological materials of others and human or animal tissue.

Biological Materials

With respect to deriving an improvement from other people's biological materials, providing the materials are in the public domain and are not protected by patents, then the person developing the improvement is the owner of and has the right to use such improvement. However, if patents exist on the original biological materials that have been improved, then although the developer of the improvement is the owner, he is estopped from licensing the improvement without right under the dominant patents.

Human Tissue

As to isolating biological materials from human tissue, there have been developments in the United States that clearly point out significant problems in this area. A patient, John Moore, has sued the Regents of the University of California for their use of tissue derived from his body for purposes of developing a significant biological invention. The university licensed the technology to others.

Moore is taking the position that the university did not have ownership in his tissue and hence he should be entitled to a share of the rewards. Granted Mr. Moore is responsible for the originating tissue; however that was taken by the university and modified to produce the cell line having interesting characteristics. To avoid confusion of this sort, it is important that in the first instance before removal of tissue from a person by surgery, one must obtain the necessary consent and release from the patient that stipulates that any tissues removed belongs to the hospital.

DERIVATIVES

In keeping with the derivation of biological materials and improvements thereto, the definition of derivatives in a license agreement can become a very difficult issue. From the standpoint of the licensor, it seeks all advantages derived from subsequent work on the biological materials transferred. The licensee, however, may have expended considerable effort. He may believe that he has made significant changes that provide a totally new use therefor, and as a result the derived material is no longer related to the original material transferred, and hence it is now outside the license agreement. The result is no payment of royalties!

The definition of derivatives is obviously going to be determined primarily by the fact situation of each licensing arrangement. It is therefore difficult to provide any standard definition of what derivative means for a particular licensing situation. However, from the licensor's standpoint, it is hoped that the net can be thrown sufficiently broad to cover all changes to the biological materials which may enhance its overall function while retaining the function of the material originally transferred. Suggested definitions for derivatives, which have been developed by the LES Biotechnology Committee, are:

1. Derivative means any progeny or subclones of parent; or
2. Derivative means progeny, clones, subclones or products of parent wherein such progeny and subclones include nonidentical progeny and subclones of parent; and such progeny includes progeny which would not have been made but for parent.

More specific definitions of derivatives are:

1. Derivative means any progeny and any genetically engineered modification that is substantially based on and incorporates an essential element of parent; or
2. Derivative means any progeny and any genetically engineered modification wherein:

Such progeny and genetically engineered modification is based on and incorporates all of the essential features of parent;

The genetic material is substantially unchanged;

The genetic material is substantially based on and incorporates an essential element of parent and is verifiably distinct from parent;

The structural and/or functional characteristics are identical to or are a predictable, expected result of genetically engineered modifications of parent;

The genetic material is substantially similar to the material from which it is derived and having a substantial portion of the characteristics of parent's genetic material;

Or any genetically engineered modification that is substantially based on and incorporates an essential element of parent without a substantial change in phenotypic expression

EXCLUSIVE OR NONEXCLUSIVE GRANT

The type of grant will depend primarily on the type of technology being offered. As already noted, should it be a "pioneer" technology, it is to the benefit of the licensor to disseminate the technology on a nonexclusive basis and at a reduced licensing fee, but yet generate a reasonable royalty return because of the broader base for marketing of the technology. On the other hand, if the technology is well developed and is of limited use the technology is probably better licensed on an exclusive basis.

FIELD-OF-USE AND TERRITORIAL RESTRICTIONS

Field-of-use restrictions become particularly important when a pioneer technology is being licensed. A basic technology may have a variety of applications. Such applications may include an immunotoxin, immunoassay, microbiological analysis, promotor, vector, animal nutrition, agricultural chemicals, energy development, petroleum products production, industrial chemicals, mineral processing, environmental controls, human and veterinary health care, and human and veterinary diagnostic care.

Rather than licensing all of these applications to one company, it is cost-effective from a royalty return standpoint to license each company to use the technology in a particular area. For example, if a vector is developed that is particularly useful for implanting different types of genetic information into a microorganism to produce corresponding products, such as various types of medicines, each company licensed would only be entitled to exploit the vector in the particular field of use.

Similarly, territorial restrictions can be set up to enhance royalty return. The technology can be licensed country by country to different companies providing there are identifiable markets in each country. This can be broken down further to identifiable regions within a country. For example, types of medical treatment could be controlled on this basis.

LICENSING FEES AND ROYALTIES PAYABLE

In view of the varied uses that biotechnology can be put to and the manner in which the products thereof can be sold, it is important to use ingenuity in developing royalty rates. The royalty scale will depend on whether it is an exclusive or nonexclusive license. As already noted in the area of pioneer technology, a nonexclusive license is preferred because of the variety of uses to which the originating technology can be put. One should consider that the royalty scale be such that it does not encourage a potential licensee to opt for the position of attempting to invalidate the patent rights, or during the contractual period, become over burdensome to the extent that the licensee contemplates litigation to break the contract.

From the university standpoint in licensing technology, neither of these options is attractive. The universities are concerned more with developing academic environment than becoming involved in costly, lengthy litigation. Continuing in the vein of licensing of university technology, it is important that the technology be transferred in a manner to provide a source of revenue.

Government grants to universities continue to be cut back. The universities must look to other areas to obtain the necessary funds to continue research. The ideal position in licensing of university technology is to have many nonexclusive licenses, each license being accompanied by a lump-sum upfront payment which is nonrefundable and not credited toward royalties. Then a reasonable royalty scale can be tuned to the manner in which the technology is being sold.

I had already referred to the interesting approach taken by Stanford University in licensing the Cohen and Boyer technology on recombinant DNA. A credit system was provided on the minimum yearly royalty of $10,000, providing the license was taken out before a particular date. This early-bird principle was successful in encouraging some 73 groups to take out a license before the due date. With respect to the royalty scale employed on the technology licensed by Stanford University, reference should be made to Katharine Ku's paper "Licensing DNA Cloning Technology" in the June 1983 issue of *Les Nouvelles*.

Royalty Scale

Development of a royalty scale for the technology being licensed will depend on how the technology is being commercialized in the particular field of use. Will there be end products made, or will the product as made be sold in bulk? Will the licensee use the technology to improve its own in-house processes of manufacture, or will the licensee elect to sell the lifeform to another, or to sell the genetic material to others?

In each of these situations, a different royalty will apply and the licensee may be exploiting the technology in all of these areas.

If the end product is sold in bulk, understandably there would be fewer units of sales. The product may be mixed with carriers or processed into some other form before it is sold to the public. A higher royalty rate should be established with respect to bulk sales, for example, 10% to 15%.

Where the licensee uses the technology to improve his in-house processing, the royalty rate should be scaled to reflect the cost saving and economic benefit to the licensee.

The outright sale of the genetic material is obviously worth considerably more. This would normally be in the form of a lump-sum payment. The dollar value affixed to that will be determined by the market demand for this type of technology, potential for its use, and its viability.

The results of biotechnology may be marketed in a variety of forms. The following are examples of suggested royalty rates for the following types of products (based on information developed by the LES U.S.A./Canada Biotechnology Transfer Committee):

—Research Reagents (e.g. expression vector, cell culture, media supplements), a royalty rate in the range of 1% to 5% of net sales.

—Diagnostic Products (e.g. monoclonal antibodies, DNA probes), a royalty rate in the range of 5% to 8% of net sales.

—Therapeutic Products (e.g. monoclonal antibodies, cloned factors), a royalty rate in the range of 5% to 10% of net sales.

—Vaccines, a royalty rate in the range of 5% to 10% of net sales.

—Animal Health Products, a royalty rate in the range of 3% to 6% of net sales.

—Plant/Agricultural Products, a royalty rate in the range of 3% to 5% of net sales.

ROYALTY RATES — UNIVERSITY VS. INDUSTRY

In keeping with the discussion of licensing university and industry technology in establishing royalty rates, some interesting information can be developed by comparing a license offered by Columbia University to a license offered by an industrial concern, Hybritech Inc. Both the industry and the university are licensing basic technology in their fields. The major distinction between these different groups is with respect to the manner in which the royalty issues as handled.

The university required a minimum yearly royalty of $30,000 even though the license is nonexclusive. The minimum yearly royalty is credited toward royalties due. The royalty rate depends upon the type of product sold, everything ranging from the final product to new genetic material. An interesting twist to the Columbia approach with royalties is that there was an early-bird special, where if you had signed up before June of 1984, a lower royalty scale applied. "Deja vu" Stanford University.

Another interesting approach in the Columbia license regarding royalties is that improvements provided by Columbia University required an additional royalty due on the benefits realized from the improvements made by Columbia. Columbia University agreed to a reduction in the royalty if the licensee had to pay a further royalty because of infringement of other parties' patents. Columbia limited the amount of reduction in the royalty up to one third of the amount of royalties due to Columbia. In other words, you could not negotiate a high royalty scale with some other group and hope to write it off against the royalties due to Columbia University. This distinction appears to indicate that the university is more prepared to accept third-party infringement and compensate for this, rather than encourage someone to attempt to invalidate the patent to avoid paying royalties.

Industrial Side

Contrasted with this position is the industrial side. Hybritech requires a license issue fee that is nonrefundable and not credited toward the payment of future royalties. The license issue fee can be broken into three annual installments. The running royalty is based on the chosen amount of license issue fee paid. The more money paid up-front, the lower the royalty rate. For $100,000, the royalty rate is 9%; for $1 million, the royalty rate is 2%.

As an enticement during the first two years of the license, the licensee can pay additional money to lower the royalty rate to the limited minimum. Nonperformance by the licensee results in the licensor, Hybritech, not collecting royalties other than the base issue fee. Hybritech agrees to the reduction in royalty if one or more of the claims of the licensed patent is invalidated. Presumably, if the product or process is no longer covered by a valid claim in the Hybritech patent, there is no need to pay further royalties. In between these areas, I am not sure how you would calculate a reduction.

From this comparison, the industrial group indeed has a higher up-front charge for technology, which may be related to the fact that it is or has been brought to a stage that can be marketed. On the other hand, Columbia University has a more guarded approach and ensures a minimum yearly income from the licensee as long as the license is in force.

The interesting result of this comparison revealed that the university is clearly oriented in a business manner toward the dissemination of technology in a way that will provide a solid return to the university.

Royalty Layering

Royalty layering can become an issue in countries where patents not only exist on the basic technology, but also protect important improvements in developing and selling a particular technology. For example, a patent may exist on the basic technology used to genetically engineer a microorganism that produces a new product. A patent would also exist on the product. A patent may also exist on special culturing conditions for the microorganism to produce the product. This patent may be held by a different company.

Furthermore, patents may exist on a newly discovered microorganism such that, when modified with the basic technology, has significantly improved productivity in making the product. Hence, a company desiring to make and sell the product under license in a country in which all three levels of patents exist, the patents being owned by different companies will result in paying two or perhaps three different royalties. The licensee is then faced with a royalty layering problem. How this is coped with will depend greatly on the ability to negotiate royalties in each instance that will permit the licensee to manufacture and sell the product at a reasonable profit.

If the licensing fees become exorbitant as required by all three different licensors, obviously the licensee will not go into business and hence the licensors will have lost the potential of licensing the technology. This will become more of a problem in the field of biotechnology as basic patents continue to issue on developments in this area and on patents on improvements to these basic developments. As this situation evolves, pressures undoubtedly will be put on the various patent holders to arrive at a fair and justifiable total royalty rate for the licensor.

CONFIDENTIALITY

Rigid controls are required with respect to the use of the biological materials and the disclosure of information to others. This is normally covered by way of confidentiality requirements in the license agreement. It is essential that all trade secrets be controlled and kept in confidence under the usual provisions respecting confidentiality. The biological materials are not to be released to any other parties without the permission of the licensor. Strict controls are to be enforced in the laboratories and manufacturing facilities to ensure that theft of the microorganisms cannot occur. Compliance with these controls must be subject to regular and frequent inspection by the licensor.

Millions of dollars can easily be involved in developing a biological application. Quite often the licensor will be very specific in requiring special types of confidentiality agreements with all employees exposed to the technical information and supervise the types of controls put in place to ensure that pilfering of the technology won't happen.

IMPROVEMENTS

In conjunction with the issue of how derivatives of the transferred material are defined, improvements to the biotechnology must be considered. The licensee may take the position that the improved change to the biological materials renders the development completely different from the biological materials originally transferred. If that is true, clearly the licensee is practicing outside of the license agreement and has no obligation to submit those improvements back to the licensor.

However, assuming the licensor can negotiate the proper but broad definition of derivatives and improvements to the original biological material, the licensor should be entitled to participate in the improvements. Such participation may be in the form of a royalty fee, nonexclusive license to the improvement with the right to sublicense other licensees then existing or in the future. In some countries, such as Canada, it is even permissible assuming it can be negotiated that the ownership of the improvements made by the licensee reside with the licensor.

One must be careful, however, to consider that in defining the conditions under which improvements are granted back to licensor that equal consideration is given to conditions that determine when improvements by the licensor are given back to the licensee. If the term "derivative" is defined quite broadly, the improvement clause includes the definition of derivative in determining what might constitute improvement. The licensor, therefore, imposes upon himself an obligation to then transfer all the improvements he develops in the parent material that will fall within the scope of the broad derivative definition. This has to be weighed against the returns that the licensor will receive from improvements made by the licensee.

ENFORCEMENT OF PATENTS

Enforcement of licensor's patent rights can be a difficult issue in the field of biotechnology. It is difficult to establish what a third party might be doing that would constitute infringement of the patent claims. It is not always easy to break down biological material to determine exactly whether the improvement, as contained in the genetic code of the microorganism, is new and infringes the patents in question.

Similarly, with the defense of third-party infringement, there are many patents issued with broad claims in the various fields of technology. These patents act as traps in covering very broad uses of some basic technology needed to prepare the next phase of the biological material program.

Since these areas can become difficult to resolve and involve expensive litigation due to the complexity of the subject matter, it is important to ensure that the issue of patent enforcement and patent infringement is clearly defined so that the parties understand their commitment to patent litigation if and when it arises.

HEALTH AND ENVIRONMENTAL APPROVALS

An area that can complicate the process of developing the technology is health and environmental approvals for use of the biotechnology. Health and/or environmental use approvals are not received overnight. They may take many months of submission, revision and interview before convincing the regulatory agencies that the biological materials are safe in the environment or safe from the standpoint of human use. Consideration has to be given to how royalty payments should be structured during this regulatory approval period that are fair to the licensor and licensee.

Reasonable assurances must be obtained from the licensee that all work conducted with the biological materials will be in accordance with safety regulations of that country to ensure that no problems or liabilities are encountered. Similarly with product liabilities, particularly in the medicinal field, the licensee must understand that they are totally responsible and will save and hold harmless the licensor from any suits which might be brought in this area.

EXPORT APPROVAL FOR TECHNOLOGY

The ability of the licensor to export biological materials and technical information to the licensee should they be foreign to the licensor must be determined. Many countries now have rigid guidelines on the export of technology embodied in technical information and products. The United States, for example, has a set of complex guidelines for the export of technical information. It can be very difficult to determine if a particular biotechnology requires approval. It is therefore important to engage counsel in the particular country to answer the relevant questions on export of the technology.

Although I have itemized and discussed what are thought to be the major issues in biotechnology licensing agreements, there are many ancillary issues to be considered, most of which are considered in standard licensing agreements. The LES U.S.A./Canada Biotechnology Transfer Committee has compiled a booklet containing biotechnology licensing agreements from several concerns, not only including the Hybritech and Columbia University license agreements, but those offered for example, by Stanford, Salk Institute, and Harvard University. Copies of these license agreements are available from the Biotechnology Transfer Committee.

Unquestionably, there are significant costs associated with the development of biotechnology, industry being in a better position to afford such developments. But universities usually provide the fertile ground for discovering basic breakthroughs in biotechnology.

Licensing offers a vehicle to acquire the technology at a reasonable cost and acquire the necessary know-how and trade secrets to commercialize products of particular interest. This is significant encouragement for universities to promote the technology they are developing in the academic search for the "riddles of life." At the same time, it is significant encouragement for industry to support research by universities and cooperate with them in this respect. The principles in conjunction with a strong patent program will lead to increased transfer of information in the field of biotechnology to satisfy mankind's quest to live!