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Science and Technology Policy: A CEO's View

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SCIENCE & TECHNOLOGY POLICY: A CEO'S VIEW

EDWARD PENHOET, PH.D.*

INTRODUCTION

I appreciate the opportunity to address the issues of patents and matters related to the Food and Drug Administration (FDA), because I think they are probably the two most important issues that face the biotechnology industry today. These two issues are not only separately important, but they are highly interconnected and I am sure you will develop that notion as you read through this Article.

I am comfortable in writing this Article because my audience seems to reflect what Chiron Corporation is today: one-third lawyers, one-third regulatory people, and a few others sprinkled in for good measure. I was asked to address several issues from the CEO's perspective. One of the things you learn as a CEO is that you should never pass up an opportunity to promote something during your talk, so I am going to start with an issue that has nothing to do with patents or the FDA, but has a lot to do with California.

THE UNIVERSITY OF CALIFORNIA, THE NIH, AND THE BIOTECHNOLOGY INDUSTRY

Oftentimes, we focus on problems of national interest and overlook our obligation to inform our various constituencies of the importance of biotechnology and other technology related industries. Recently, I had the opportunity to present a talk to the Board of Regents of the University of California. Unfortunately, they were as ignorant as most people about how important biotechnology has become to California and what an extremely important role biotechnology has played in the development of a large portion of California's economy. In particular, they seemed to ignore how important the University of California has been in the development of this entire field. So Figure 1 simply illustrates the UC connection with the biotechnology industry.[1]

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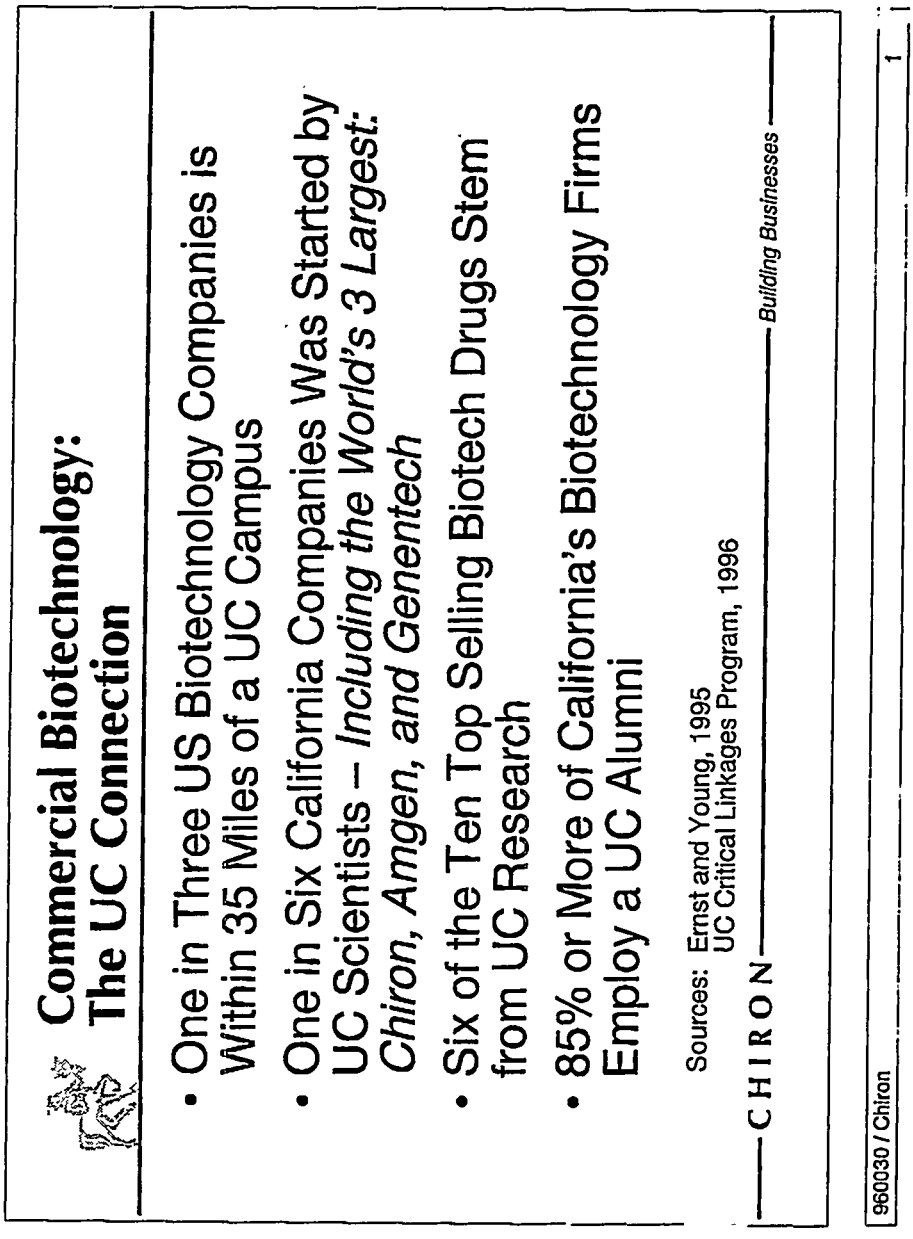
1. It is particularly appropriate that this Article was originally presented before a meeting at a UC facility and sponsored, at least in part, by a group of UC people.

FIGURE 1


Commercial Biotechnology:
The UC Connection
• One in Three US Biotechnology Companies is Within 35 Miles of a UC Campus
• One in Six California Companies Was Started by UC Scientists – Including the World's 3 Largest: Chiron, Amgen, and Genentech
• Six of the Ten Top Selling Biotech Drugs Stem from UC Research
• 85% or More of California's Biotechnology Firms Employ a UC Alumni
Sources: Ernst and Young, 1995
UC Critical Linkages Program, 1996
CHIRON
Building Businesses
960030 / Chiron
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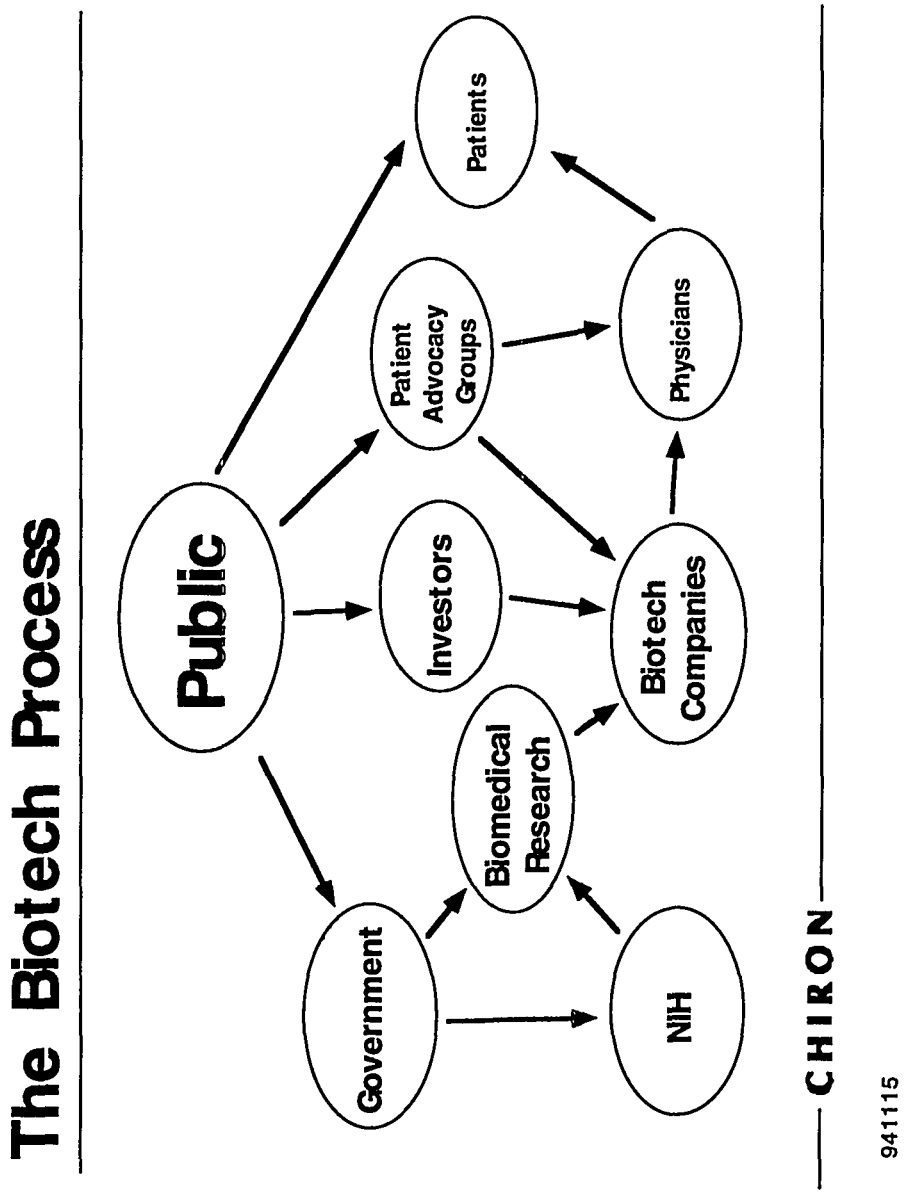
One in three biotechnology companies in the United States, which is practically one out of three in the world because there are very few biotechnology companies outside the United States, is within thirty-five miles of a UC campus. One in six of these companies was started by UC scientists, including the top three: Genetech, Amgen, and Chiron. Six of the top ten best-selling biotechnology drugs stem from UC research, most of them developed by California companies, eighty-five percent of which employ alumni from the University of California. Thus, there is tremendous historical cooperation between the University of California and the biotechnology industry. Although many of us discuss this issue frequently, it is not as widely understood as it could be and I think that as we grapple with problems of significance to the biotechnology industry, we must also continue to develop programs which further enhance the relationship between the University of California and the biotechnology industry, especially the industry within the state of California.

Figure 2 indicates the complexity of the whole field of biotechnology. It focuses on the role that the public, and the public as represented by many constituencies, has played in the development of the field.

FIGURE 2


The Biotech Process
Public
Patients
Patient Advocacy Groups
Physicians
Investors
Biotech Companies
Biomedical Research
Government
NIH
CHIRON
941115

As you can see in Figure 2, the government obviously plays an extremely important role in this field. This is an enormous area that each of us views from the perspective of our own interests. But stand back and try to analyze all the ways in which the government influences business in this country: local governments decide whether we can build a new laboratory or not; the state handles this relationship with companies in a variety of different ways; and at the national level, patents, tax law, and the FDA, all have a profound influence on the biotechnology industry. These are all extremely important issues. Of increasing importance is how we handle all of this within the context of trade and commerce overseas. Thus, the government is truly our partner in the biotechnology business. There is no question about the fact that the government influences everything we do. And it begins with government supported research.

Investors are also extremely important. At its core, this industry is comprised of two things: science and money. These two things must work in concert with each other in order to bring useful new products to the marketplace. The interrelationships between the availability of capital and the availability of science are extremely important and are highly affected by patent law and the behavior of the FDA. On the right hand side of Figure 2, we get closer to the patients, and the way these patient groups are organized has a strong influence on the capital which is available and coming into the industry.

If we look for a moment at what have been the key factors in the rise of biotechnology industries, we arrive at the same conclusion: funding from the National Institutes on Health (NIH). This is not a forum to discuss NIH funding, but it is an extremely important part of our industry. For example, tax laws, such as those pertaining to research and experimentation, have a measurable and meaningful effect on the research and development pipeline of products in our industry. Yet they are dwarfed by the subsidy we get as an industry, and we should call it what it is: It is a federal subsidy to our industry, supporting primarily NIH funded basic research in the biomedical arena.

The reason biotechnology exists in the United States, the reason it thrives in California, has more to do with NIH funding of academic research than any other single factor in our industry. It is an indirectly subsidized industry in the sense that it provides the intellectual framework for the development of the entire industry. Nevertheless, the reason that biotechnology companies are located close to University of California campuses is that those campuses are the wellspring of the new technology which forms the basis of, and in many cases, the founding and maintenance of these companies.

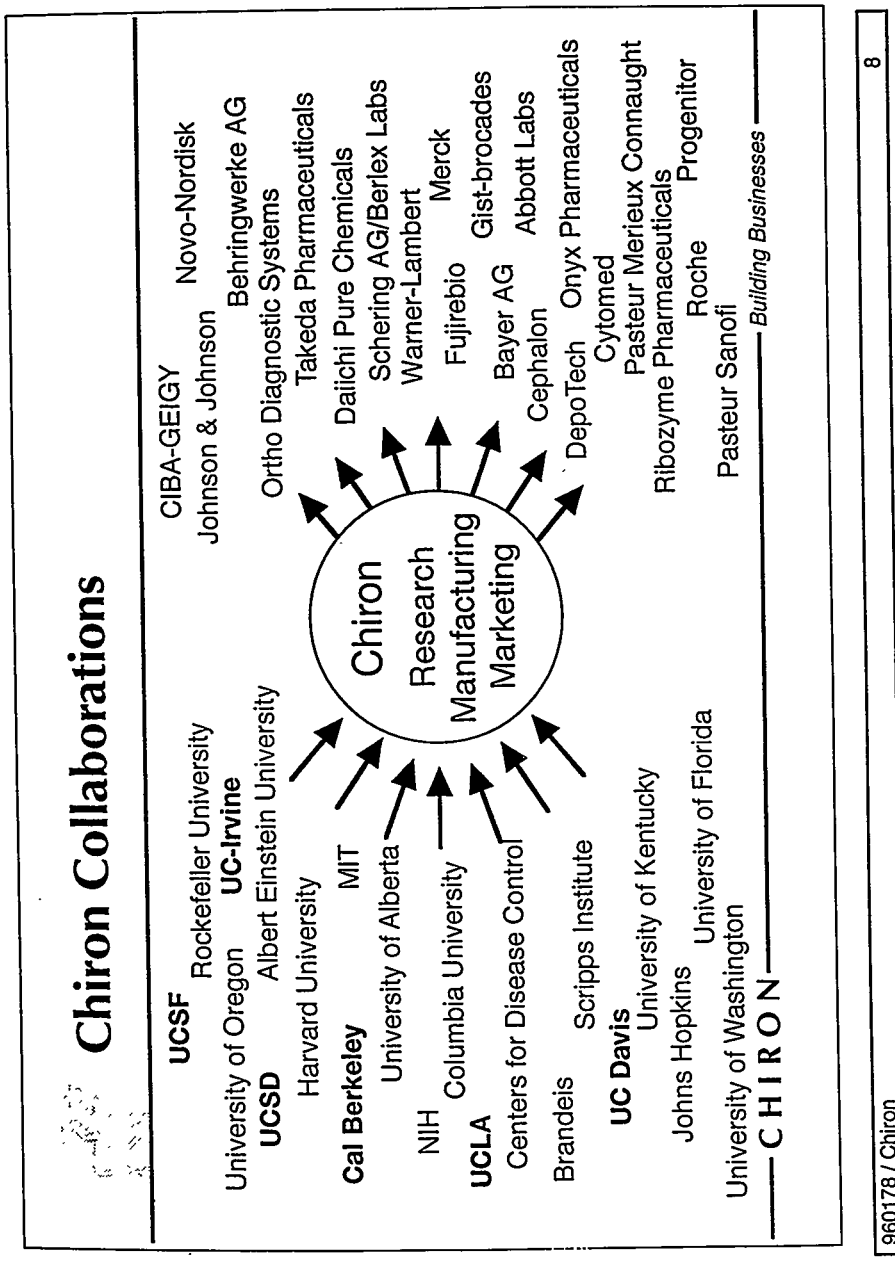
The reason that biotechnology is primarily a United States phenomenon is that the United States is where the technology was originally developed. It is also an area where sufficient capital is available to fund these kinds of things. These are almost inextricably linked to each other as a phenomenon. The reason why most multinational health care companies are moving the base of their research to the United States is that this is where the scientific

base is, and this is a phenomenon particularly true of the UC system for some time. A majority of the major German pharmaceutical companies are moving the headquarters of their research firms to the United States. The Swiss companies are slowly, but surely, doing the same thing. They are not explicit about it because it causes them political difficulties at home, but more and more investment by companies from all over the world is being concentrated in the United States because the intellectual property is located here. Our intellectual property is still largely resident in NIH funded laboratories around the country and most of those are obviously within the university environment. It is important, therefore, that this relationship be maintained, that the NIH continues to receive adequate funding. This is much more important to us than are minor enhancements in the tax law intended to benefit research. For me, it is the most important single issue in terms of the technology that is continuing to drive our industry.

The investment of the NIH, now close to $12 billion a year, is exceeded only by the investment of the industry in research and development, which is about $20 billion a year. There is an important difference between investments made by the government and those made by the industry itself. The industry is stepping up the challenge of turning basic research into useful products by spending more than the government spends. But most of the $20 billion spent by companies today in research and development is development dollars, not real research dollars. Companies do not engage in much basic research, so that engine is extremely important to progress. We must never lose sight of this fact because without the support of the NIH, I think the industry would be in a much less desirable situation than it is today.

Those at the top of the financial pyramid say technology is what drives the industry; those at the bottom say you cannot get very far with technology unless you have the money to develop it. The monetary issue simply shows that in one company's case, Chiron's, how aggressively we utilize relationships with academic institutions as sources of technology for our company. Figure 3 highlights all the University of California campuses with which we do business.

FIGURE 3


Chiron Collaborations
UCSF
Rockefeller University
University of Oregon
UC-Irvine
UCSD
Albert Einstein University
Harvard University
Cal Berkeley
MIT
University of Alberta
NIH
Columbia University
UCLA
Centers for Disease Control
Brandeis
Scripps Institute
UC Davis
University of Kentucky
Johns Hopkins
University of Florida
University of Washington
CHIRON
CIBA-GEIGY
Novo-Nordisk
Johnson & Johnson
Behringwerke AG
Ortho Diagnostic Systems
Takeda Pharmaceuticals
Daiichi Pure Chemicals
Schering AG/Berlex Labs
Warner-Lambert
Merck
Fujirebio
Gist-brocades
Bayer AG
Abbott Labs
Cephalon
DepoTech
Onyx Pharmaceuticals
Cytomed
Pasteur Merieux Connaught
Ribozyme Pharmaceuticals
Progenitor
Roche
Pasteur Sanofi
Building Businesses
Chiron
Research
Manufacturing
Marketing
960178 / Chiron
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Again, this was for the benefit of the Regents of the University of California, so the illustration has an obvious bias. Nevertheless, it is also a reality that more than half of Chiron's support for university based research and relationships to collectively build value goes to University of California campuses. That is of course partly due to the fact that I came to Chiron from UC Berkeley and Bill Rudder came to Chiron from UC San Francisco, but I think we are fairly typical of people who have migrated in that direction. This is actually a very small fraction of the total number of relationships that Chiron has with university laboratories. Today, we have some 500 collaborations with university laboratories.

It is important that those relationships continue to develop, but it is also important for the technology that arises from those relationships to be protected by patent. Without patents, the technology has little or no commercial value. I will return to that point later, but I do think that today, unfortunately, we do not have the most effective and seamless strategy between the generators of technology, the universities, and the exploiters of technology, the companies. We do not have as effective a mechanism for protecting the overall package of technology generated as we potentially could have. I think it remains a challenge for us to figure out a better way to develop communally strong propriety positions. This remains a significant challenge.

Since its beginning, the biotechnology industry has been totally dependent on the availability of capital. Unfortunately, the availability of capital undergoes very wide swings of interest. In the past fifteen years that I have been involved in this business, we have seen about six cycles of feast and famine with respect to investment capital. When we started the company in 1981, it was easy to get funding. Basically, you could stand on a street corner where some venture capitalists would walk by and say, "I have a Ph.D in biochemistry, and I want to start a biotech company." You could have collected the money on a street corner. The next year, just one year later, it was almost impossible to raise any money. The year following that, there was again tremendous interest. All biotechnology companies, including Chiron, went public and raised money. Two years after that, the industry was again in the doldrums.

To some degree, this scenario is irrational, but it is also predictable because of the excesses in this field. However, if you look at the availability of venture capital for biotechnology over a long period of time, you find that it is driven by factual analysis. Today, factual analysis of the prospects for commercial success of the biotechnology industry is increasingly important. There is plenty of capital in the world; the world is awash in capital in a way, but it is looking for homes around the world where it can be multiplied and where people can make the best use of the capital. In the United States, especially in California, these are the kinds of things that affect decisions to invest in biotechnology.

Health care reform and managed care have clearly been factors which helped define the marketplace for biotechnology products. As a result, these

products experienced tremendous scrutiny during a time when policymakers were examining health care costs and the profitability associated with the industry. Speculation as to regulatory reform made investors nervous about investing in health care companies, including biotechnology stocks. Thus, that was a period in which the industry experienced the pressure of a scarcity of investment capital.

Budget constraints in the United States also affect the underlying financial support for our industry. We were very fortunate to have modest increases in NIH funding this year in the budget,[2] but we cannot continue to count on such increases in the future. We are probably facing a constrained future with respect to NIH funding for basic research in this country. In spite of a modest increase this year, the prospects of fairly flat funding for the next few years after that will force us to live with more constrained funding of basic biomedical research.

Finally, new technologies obviously impact the public interest whenever scientists discover something exciting and new that appears to have commercial utility. One thing we have learned in recent years is that many in the general public are interested in biotechnology now, so these discoveries are often published in the newspapers. For example, most of us have read about the cancer genes discovered recently, as well as a variety of other new things. The general public learns about new developments in biotechnology quite quickly and this information tends to stimulate general interest in the industry. Consolidation from the pharmaceutical industry is an important element in all of this.

PATENT LAWS AND PROBLEMS

Issues related to patent law, particularly those relating to the General Agreement on Tariffs and Trade (GATT), the North American Free Trade Agreement (NAFTA), and the FDA's orphan drug status are extremely important in determining the availability of capital for biotechnology. In the past, this has been to some degree an arcane area. Studying patents has never been something that has appealed much to the general public or to the investing community. In recent years, however, the patentability of products in our field has become a dominant factor in analyzing the value that is created in the biotechnology industry.

As we speak today, we have a situation in biotechnology in which about 85% of all the biotechnology products on the market today are protected by patents. The largest products—erythropoietin, G-CSF, interferons, (alfa and beta interferons), hepatitis C tests, tissue plasminogen activator (TPA), and growth hormone—are all covered by patents. In aggregate, they represent sales of close to $10 billion a year. It has become a very large industry.

2. *See* Anthony S. Fauci, *Biomedical Research in an Era of Unlimited Aspirations and Limited Resources*, 348 LANCET 1002 (1996).

However, it is a very small number of products. This $10 billion a year in sales comes from a relatively small handful of products—only twelve to fifteen products. Without patents, those twelve products which have sales close to $10 billion a year today would be likely to have sales close to merely $1 billion a year. The profitability of this industry, its ability to support further research and development, and its ability to attract further capital would be devastated if these products were not afforded patent protection.

If you look at the history of biotechnology, the most important single factor that has led to the health of the industry today is the realization in the second half of the 1980s that biotechnology patents would be issued, would be broad enough to be useful, and would be sustainable in the courts.[3] It took a fair amount of litigation; it still does. Anytime you have anything of value, people will fight over it—that's a given. But during the period when biotechnology first started, there were many questions about whether biotechnology patents were going to have any value. Many remember that era. In the last half of the 1980s, that question was answered[4]: Yes, they have value. They have value not only in the sense that people can get patents, but their claims are broad enough that they give them useful protection in the marketplace,[5] and that is what we have to keep our eye on. If you do not have useful protection in the marketplace, a patent is simply a lovely piece of paper that you can frame and put on your scientists' CV; but it has no commercial utility unless it gives protection in the marketplace.

I want to spend a minute on this issue because I think that the most important positive factor in the past has been the development of utility in the marketplace. The biggest rut we face as an industry today is the possibility that utility in the marketplace will be gutted by the agreements we have reached in the GATT agreements around the world.

Interestingly enough, biotechnology patents have in a strange way become more valuable than traditional pharmaceutical patents. Historically, everybody thought that pharmaceutical patents were valuable for protecting their new chemical entities. But chemical entities tend to be afforded rather narrow protection, and we learned that they are fairly easy to design around. The result of this is that the traditional pharmaceutical industry today has many patented compounds, but tends to sell them in a quasi-generic marketplace. The interesting thing about knowledge is that if you and I understand the same set of facts, it is almost always true that we can independently come up with a unique solution to a problem. With small molecules and narrow patenting of those molecules, we have seen the situation where each company in the market of small molecules[6] files a

3. Scripps Clinic & Research Found. v. Genetech, Ind., 927 F.2d 1565, 18 U.S.P.Q.2d (BNA) 1001 (Fed. Cir. 1991).

4. *Id.*

5. *Id.*

6. *E.g.*, ACE inhibitors and h2 antagonists.

patent on its individual compound. The market then becomes somewhat generic because there are many similar compounds which do not infringe the other patents and can therefore also enter the marketplace. So, pharmaceutical patents have become less valuable and biotechnology patents have become more valuable because it is much more difficult to engineer around patents on complex macro-molecules such as proteins.[7]

From Chiron's perspective, the twenty-year patent term enacted as part of the GATT agreement[8] is devastating to the biotechnology industry. This bears repeating: In our view, the twenty-year patent term enacted as part of the GATT agreement is devastating to the biotechnology industry. The reason for this has to do with timing and the relationship of timing to the FDA process for approval. First of all, the Patent and Trademark Office (PTO) is very slow to grant patents in biotechnology. Thus, the biotechnology companies face the very real prospect that a patent application may sit in the PTO for half of its patent term before a patent is actually issued. For example, we at Chiron discovered hepatitis C in 1987. Today, almost ten years later, we have only a very narrow patent issued by the PTO on hepatitis C. This is happening, by the way, in an environment where we have many patents issued around the world, in Europe and even in Japan.

Half of the newly defined GATT term, which gives twenty years from the time an application is filed, will have already been used up in the PTO and we still do not have a patent issued. It is also true that we are in a highly complex field and we expect that there will be many interferences until all of this is resolved. Even when you receive a patent, more commonly than not, it provokes interference from other people who may or may not have legitimate claims to that technology. Such interference consumes yet another ten years. It is quite conceivable that the patents on many valuable inventions will expire before they ever attain a situation where they have market exclusivity, the very asset which a patent is intended to secure.

We at Chiron strongly support efforts to either create a patent extension which takes into account the time in the PTO and delays due to interferences or appeals, or to revive the Dole-Rohrbacher Act[9] to restore the seventeen-year patent life after the patent is issued. We support these efforts because we can easily foresee a situation where the issuance of some patents will be delayed, especially for those products which take ten to twelve years, sometimes longer, to develop. For example, consider beta-interferon, which we developed with our partners at Schering and Schell as a treatment for multiple sclerosis. Beta-interferon was cloned and expressed in 1980. It reached the market for patients suffering from multiple sclerosis in 1994.

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7. The larger the molecule, the more difficult it is to determine the relationship between structure and activity and also the more difficult it is to make non-obvious changes in structure without losing the desired activity.

8. General Agreement on Tariffs and Trade, *opened for signature* Oct. 30, 1947, 61 Stat. pts. 5, 6, T.I.A.S. No. 1700, 55 U.N.T.S. 187.

9. 35 U.S.C. § 154 (1983).

After fourteen years of hard work, investment, and development, the new twenty-year patent term would have cut our protection to a mere five years of market exclusivity for a product that cost us hundreds of millions of dollars to develop.[10] No one is going to undertake a very long development program in the future if they face the prospect of a long and uncertain development period, followed by the expiration of the patent clock. People will discontinue their developments after six or seven years because it is simply not worth the risk to continue. This will destroy the patent's value and inhibit the development of useful medicines because people are not going to undertake these developments if they are not guaranteed adequate protection when they finish.

Another extremely important issue relates to how we handle the approval of biotechnology products. This is obviously directly related to the FDA because of the degree to which the FDA makes the process of approval cumbersome. One must remember that it is not just getting FDA approval which makes it cumbersome; rather, it is the whole process from the very beginning that makes it cumbersome and time-consuming. If we could streamline the FDA, this problem would be much less acute than it currently is. It is the long periods required for the FDA, combined with the long periods required for the patent process, that destroy a product's value in the end.

The other extremely important patent issue is what happens to our products overseas. We are in a situation where we allow other countries to manipulate the patent laws to their own benefit and give such narrow claims to United States companies so as to destroy the commercial utility. For example, in Taiwan, a patent office board of appeals recently ruled that Chiron's HCV patent claims could only cover a diagnostic test, using a recombinant protein, expressed from a clone obtained from a chimpanzee in the United States.[11] This does not speak at all to the issue of our invention. Instead, it speaks to a very narrow and self-serving interpretation of the spirit of patent laws around the world to help just one municipality.

We think the patent issue has both good and bad associated with it now. We have had a good history, but we are on the cusp of entering into a terrible era, and I think we must work extremely hard to avoid that. We view this as the most important single issue, and it amazes me how little energy and time, given the importance of this problem, the industry as a whole is investing in this matter. Nobody seems to want to tackle this issue vigorously, but it is a tremendously important matter.

The other problem is the FDA. There have been some good developments happening at the FDA. One very positive thing is the FDA's willingness to change their manufacturing requirements and approve the so-

10. A new bioengineered drug typically costs $100 million to $150 million to develop. David R. Olmos, *Suitor for Chiron May Be CIBA-GEIGY*, L.A. TIMES, Nov. 15, 1994, at D3.

11. BIOTECHNOLOGY INFORMATION INSTITUTE, HEPATITIS C PATENT DISPUTE (Feb. 1995).

called "well-characterized" biological products.[12] These changes allow a company to alter its manufacturing technologies and then so long as the company can prove it has the same product, sell that product instead of the one approved with the original manufacturing technology. This speeds up development because in the past, you had to have a fully developed process for your molecule in place before you could start clinical trials. If you wanted to change your process, you had to repeat all of the clinicals. This is an extremely valuable change in the FDA regulations that will expedite the process tremendously for biotechnology companies, making approval much less expensive to pursue.

Although I think this is a very positive move for the FDA, we think the FDA can move farther. We have seen some movement now in cancer drugs, getting tentative approvals on the basis of Phase II data[13] showing tumor shrinkage.[14] It is a very positive move in our regard. We hope that the FDA will further relax its manufacturing guidelines because many of those guidelines force us to manufacture our products outside of the United States instead of manufacturing them here at home. In fact, many companies have a two-tier system: They manufacture in other countries for products sold throughout the world, but manufacture in the United States for products sold in the domestic market. This is tremendously inefficient and consumes money that could otherwise be utilized for research and development. Chiron applauds any FDA reforms that make the process more simple and more straight forward.

We think the federal government, however, does have a legitimate role to fulfill in ensuring that the American public gets products which are safe and effective. We are not arguing that the FDA be disbanded entirely in favor of a free market for these products. That would go beyond what we would like to see. But there is a tremendous opportunity for simplification and better scientific tools to enhance such simplification.

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12. "Well-characterized" biological products are those biotech products whose "identity, purity, impurities, potency and quality can be determined and controlled." Steve Sterberg, *Three Days of Debate Yields Possible Consensus on FDA Definition for Biotech Products,* Bioworld Today, Dec. 14, 1995, *available in* LEXIS, NEXIS Library, Magazine file.

13. Phase II includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. 21 C.F.R. § 312.21 (1996).

14. *Biotech Financing in First Quarter '96 Outpace Prior Three Months, Exceeding $1.6 Billion,* P.R. NEWSWIRE, Apr. 4, 1996.

TAXES AND THE BIOTECHNOLOGY INDUSTRY

The final issue of importance is taxation. The federal research and experimental credits legislation[15] is a benefit, although not a tremendous benefit for most biotechnology companies. There are many issues in the way it is calculated, with a so-called base that is determined by sales.[16] Most early stage biotechnology companies do not have any sales. This results in a very uneven utilization of this tax credit. Unfortunately, most of the benefits from this credit do not go to truly innovative companies. It would be nice if these types of tax credits actually stimulated innovation instead of giving benefits to large companies. It clearly has not worked tremendously well. The United States investment in research and development has shrunk from 3% a decade ago to 2.6% in the last year,[17] so we need to do a better job of stimulating research and development. I am not sure that this tax credit alone will be a major factor in this; but it has certainly been helpful.

Finally, most biotechnology products today are quickly utilized around the world and, therefore, many successful biotechnology companies set up international operations. We have to be careful that our tax laws do not stimulate those companies to invest in overseas research and development, rather than in the United States. It is quite technical, but there are some aspects of tax deferral for foreign subsidiaries that encourage United States companies to go incur research and development expenditures outside of the United States so that they can get tax benefits in those local environments. Because of this, I believe there will be a trend to do more research and development in Europe. Currently, everyone is coming to the United States, but at the same time, there are some big benefits now for doing research and development in Europe[18] and those benefits will increase in the future. We as a nation must try to keep as much research and development as we can domestically, and not create tax situations that encourage organizations to move their research and development operations outside of the United States.

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15. 26 U.S.C. § 41 (1996).

16. The section 41 credit is incremental, amounting to 20% of the excess of current qualified research expenses over a base equal to the mean of qualified research and experimental expenditures for the preceding three years. *Id.* at § 41(a)(1)(c). If there have been no research and experimental expenditures in any of the preceding three years, the base is 50% of the current year's expenditures. *Id.* at § 41(c)(3).

17. *See* Gattelle, *R&D Magazine Forecast Predicts Small Increase in R&D Expenditures for 1996*, ELECTRO MANUFACTURING, *available in* LEXIS, News Library, Magazine File.

18. One benefit, for example, is that it is easier to initiate human trials. Also, the trials cost significantly less because hospital and physician services costs are significantly lower in Europe than they are in the United States.

CONCLUSION

So, that's my soap box for the time being. I was asked to give a CEO's perspective, and that's what I've tried to do. I appreciate this opportunity. I think that it is important that those at the United States Patent and Trademark Office fully understand the effects of the twenty-year patent. Although what they have done appears to be quite logical and nothing is inherently wrong, I think that they do not truly understand the double bind we are in as a result. Therefore, I think communication is an important issue. I think we need to press all of our organizations, Biotechnology Industry Organization[19] and otherwise, to work even harder on this matter than they already have. Some of my colleagues have been somewhat intimidated about this matter because it has a lot of political support from other industries in the United States, but I think just promoting the realization among our colleagues of the urgency of this issue is really important because the twenty-year patent term and NAFTA as part of the GATT agreement is devastating to the biotechnology industry. Unless meaningful reforms are initiated soon, the United States' progress in biotechnology will be greatly retarded.

19. The Biotechnology Industry Organization (BIO) is a major trade association comprised of approximately 560 biotechnology companies.