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International Challenges for the Pharmaceutical/Biotech Industries in the 21st Century

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**2003 STANFORD LAW &
TECHNOLOGY ASSOCIATION
CONFERENCE:**

**IDEAS WITHOUT BOUNDARIES:
CREATING AND PROTECTING
INTELLECTUAL PROPERTY IN THE
INTERNATIONAL ARENA**

**INTERNATIONAL CHALLENGES FOR THE
PHARMACEUTICAL/BIOTECH INDUSTRIES
IN THE 21ST CENTURY†**

*John Barton, Moderator**
*Donald Francis, Panelist***
*Stephen Maurer, Panelist****
*Harinder S. Sikka, Panelist*****
*Vernon M. Winters, Panelist ******
*Dr. Herwig von Morze, Panelist******

MR. BARTON: When Darrius asked me if I would chair a panel on my favorite subject, it was very easy [for me] to say yes. I think this is my

† On March 15, 2003, the Stanford Law and Technology Association (SLATA) presented a symposium on creating and protecting intellectual property in the international arena, or “Ideas Without Boundaries.” The following is an edited version of the transcript from the conference panel and discussion. More information about SLATA and its conferences can be found at <http://slata.stanford.edu>.

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favorite subject, both because I enjoy the technical issues, and because it's the most important one that I know of. We have a system that is absolutely wonderful [at] producing medicines and treatments and vaccines for certain diseases of importance to certain of us in the developed world, and absolutely lousy for producing products for anything else. And the patent system plays a role in this. Finance plays a role in it, most of all. Our understanding [and] what we are trying to do in health care plays a role in it, but it certainly, in my mind, is one of the most important problems we have.

We have an absolutely wonderful panel and I'm not going to take significant time [with] the introductions. I assume you all have the biographies, don't you? I'm not going to take significant time [with] the introductions, simply to give the speakers more time and give more time for questions; because I have been very nasty to them about how long I'll give them and about speaking over the time limit and all that. So let me begin then initially with Steve Maurer, Lecturer in Public Policy at U.C. Berkeley, who will give us our first presentation.

MR. MAURER: Well, that's the hardest part of the talk So indeed, we have this problem that we do very well at [providing] medicines for the first world, and we have Intellectual Property ["IP"] to thank for that. What are we doing wrong elsewhere and can we tinker with it? Very quickly, the point of the talk is I'm going to review for you that IP has costs as well as benefits. These are very well known. You can quote Jefferson to this effect, and their powerful generalizations that the economists have done on IP's costs and benefits and when it's the best tool in the 20th century. The third world is a very peculiar environment for IP. A lot of the usual assumptions don't work very well. We'll review that. And then I'll talk about proposals that mostly economists have made to improve the system. This is an outgrowth of the fact that they've built all sorts of elaborate models about how to improve IP itself. But, this is a special class of models tailored for the third world. And finally, I'm going to ask is this task hopeless? Would it be better just to do something with a non-IP model? And I'm not going to decide that, but I think there's a reasonable question there.

First of all, just to review, the man in the street basically thinks that the problem with monopoly is that it makes the man in the corner there rich. That's not a very appealing view to an economist because in theory you could tax Bill Gates and put his money back in the economy and everything would be fine. That doesn't happen in life, but it happens in theory so they don't worry about that. They say that's just a distributional issue. What they really care about is that monopolies are inefficient. And

they mean inefficient in the special sense that, is it possible that if we rearrange the economy, Bill Gates would be no worse off and other people would be better off? In that sense, the economy is inefficient if everybody could be at least as well off and somebody's life could be improved. And this is the only graph I'll show you, but it's worth looking at. A is the so-called market solution, where a lot of people buy the product at a cheap price. B is what a monopolist would impose. A patent gives you the power to do a monopoly. And the thing labeled "dead weight loss," economists come up with such lovely transparent definitions, are the number of people who are deprived of the product because it's priced at B instead of A. The one thing I want you to notice about this graphically, and then I'll stop, is that it depends on the flatness of the demand curve. If this is a very steep curve, dead weight loss is small, but if you have flat curves, like you do in the third world, like you do if the global economy has both lots of poor people and lots of rich people, dead weight loss becomes an important drawback to using IP.

So, what's good about IP? What's good about IP is it gives people outside the government who have information that the government doesn't have, incentive to use their information in picking the next research project. And the two classic kinds of information that people may hold is, first of all, we don't know that all products are something we'd even want—that if I built this thing the market would come. It's usually not a problem for medicine, but I . . . imagine a Bob Newhart skit in which the Botox people go to a venture capitalist and say, look this stuff will paralyze your face and people are going to buy it like crazy.

(LAUGHTER)

I would've wondered. I'm not that smart in prospect. I knew in hindsight it was a great product. Scientific risk is what you're usually worried about in this category. Nixon announced a disastrous war on cancer in the 70's on the theory that [it] was like the Manhattan Project. If we only threw enough money [at] it, we were just about there. But there was no real judgment about where to get started. Everybody had a pet judgment. There was no obvious consensus that this is the thing that we need to do, and so we spent a lot of money and we still have cancer. At the other end of the extreme, we have gene sequencing. Leroy Hood built this machine that sequences genes and if you decide that a particular chromosome is something that you'd like the intellectual property on, you basically set their machine running and go home. Now I'm sure that's an insult to the biologist, but it's a good 30,000 foot view of the system.

Alright, what's strange about the third world from the point of view of engineering IP? First of all, there's no money in Africa, right? Normally IP

gives consumers a vote—that's the great thing. In Africa, by some estimates, the amount of medical care that is needed in sub-Saharan Africa per capita exceeds the gross domestic product per capita south of the Sahara. There aren't enough people to have the votes to say, "yes, we need these third world medicines." That's the very simplistic reason why IP doesn't work in an unaltered form. The second reason is there's not enough money in Washington. We consistently under-fund third world budgets by very paltry amounts, and the recent Bush speech gives people some hope, so maybe there's news in that. But we're always going to live in a world where Washington is under-funding this in terms of you know, you sort of look at the paper, and go, geez, why don't we spend 1350 a head to do what we should, which is what these numbers typically come out to. And finally, as I've already mentioned, in the West, demand is very inelastic, very steep at the demand curves. Why? Because we're all insured, and it's like, sure, give me the best drug. That's not true in the third world.

Okay. So there [are] two types of diseases to begin here. One is, there are diseases that have a presence in the West, and those we're very good at developing cures for. And can the free world sort of free ride? The third world has between half and two percent of the world pharmaceutical markets. If they free ride, nothing happens basically to first order . . . the incentives of the drug companies. So what we want to do is set things up so they can get access to it, but we don't interfere with the markets in the first world which is what's driving the innovation machine from a patent standpoint. There's been a suggestion by Patricia Danzon, that, you know, TRIPS [Trade-Related Aspects of Intellectual Property Rights]¹ allows parallel imports.² We ought to have a rule so that you don't have a lot of imports going back and forth between the third world and the first world. Why? Because that will drive third world prices to first world prices—bad idea. John Barton, I'll let him talk to that, has said, you know, we need to have to tiered pricing in the third world. There have been various articles like that. And finally, Jean Lanjouw has kind of a cute paper, that says when you ask the U.S. Patent Office for a license to file for patents abroad, you need to promise them that you won't use it to purchase—to shut down third world drug companies.³ And if you promise that, then basically what

1. See Agreement on Trade-Related Aspects of Intellectual Property Rights, http://www.wto.org/english/docs_e/legal_e/27-trips.pdf.

2. See Patricia M. Danzon & Adrian Towse, *Differential Pricing for Pharmaceuticals: Reconciling Access, R&D and Patents*, AEI Brookings Joint Center (2003), available at <http://aei-brookings.org/admin/pdffiles/phpng.pdf>.

3. Jean Lanjouw, *A New Global Patent Regime for Diseases: U.S. and International Legal Issues*, 16 HARV. J.L. & TECH. 85 (2002).

you do is you give up having your patents in the underdeveloped world and you only have it in the first world or visa-a-versa. Okay.

There's some good things that are coming out. Pharmacia recently made a deal that said look, if you produce my drugs in a different shape and color that makes it harder to ship it back to the first world. I'll let you use it in the third world.

Right now drug prices are pretty low—90 to 97 percent off in Africa. And there's even a recent paper that was quite controversial that says maybe patents don't matter. A lot of drugs are not patented in a lot of African countries. The problem is that a lot of this exists because there's basically no money for drugs in any case. If we start solving the problem and there's serious money for drugs in Africa, maybe people will start patenting. Maybe prices will rise.

The real peculiar problem is tropical diseases. [That is] about half or a little more than half of the total problem, if you're saying let's save peoples' lives. And there are various proposals that have come out in order to [determine whether] we [can] make the invention machine work for the third world? And they all involve the first world putting up money to simulate third world demand, because there isn't any money in the third world. One is you'd have a prize for the guy who comes up for a malaria vaccine. Another one is you could have a fund that promises in the future if you build a malaria vaccine, we'll pay for it. We'll buy so many thousand at such a price, so many million at such a price. There's the defend proposal: We'll buy a license for the third world. The first world will continue to have high prices but we'll buy a low price license for the third world. And finally, there's kind of a cute thing from a WHO [World Health Organization] official that says, look, we'll give you an extension on your first world drugs that you really are making money off of, if you'll give the third world drug away for free. All of these things have both an economic component, which I think you understand now, but also political component that they usually more or less explicitly involve hiding the price from Congress. And as I say, so these figures give you some sense of just how far apart things are. But there's some reason to be a little bit cheerful that Congress will put up some money in light of the Bush initiative,⁴ and so the question is, where are we?

If you want the absolute cheapest solution, IP has this built-in monopoly. It brings me back to the uncool version of what's wrong with monopoly. It raises prices. If you want the absolute cheapest solution, you

4. See President Bush's AIDS Initiative, Foreign Press Center Briefing, U.S. Department of State (Feb. 6, 2003), at <http://fpc.state.gov/17497.htm>

should not give out an IP monopoly. You should pay people to do the research. Pay somebody in the National Lab to do it. And in fact, if it turns out that IP will always be more than what Bush is willing to write a check for, I would say, hey, let's go to the National Labs and have them do this project. When I talk to people in the labs who say look, we can come up with the targets, we can come up with the chemicals. We can't do trials, but you can pay the drug companies by the hour to do trials. So, is this a sensible thing? Should we opt out of IP? There are stories both ways. One story is, USAID had a horrible scandal in the '80s that involved both sides of the transaction sleeping with each other and they have tried three malaria vaccines, none of which worked—utter disaster, waste of money. On the other hand, there's the polio example. In the 1950's, March of Dimes paid two million dollars to researchers. They came up with a vaccine, and there was no intellectual property on it. The pharmaceutical companies got into trials. They did it at cost and very successful. Something we're very proud of. So this can be done. And given that it's such a marginal case to use IP, if we can't hide the budget figure from Congress, we got to pony-up, then I think we need to get out of the IP game. And that's it.

MR. BARTON: Thank you very much for an excellent introduction. Let's turn from the broader level to the more IP oriented level with Mr. Harinder Sikka, Senior President for Corporate Affairs of Nicholas Piramal, India Limited. I'll turn it over to you.

MR. SIKKA: Thank you very much, John. I will cover most of India's concern or developing nations concern on the recent TRIPS that has been blocked about the compulsory licensing and the issues concerned thereof, black marketing concerns which have been raised left and right, the solutions thereof as far as a developed nation is concerned, from the differential point of view, differential pricing, as well as through research and development. Let me come to—straight away to, most countries, developed countries believe that TRIPS talks about a particular disease or a set of diseases. The U.S. has said that there are so many numbers of infectious diseases that it should be incorporated and no more. TRIPS does not talk about a particular disease. It talks about health care as a whole. It also does not define a national emergency. As per India, it is left to each country to decide which way to go about it and how best to go about it. The main aim of TRIPS in public health care is to provide the technology, is to provide a life saving drug to each human in a poor country. And in its present form, TRIPS does not support technology transfer. It at best favors IPR. One of the chief reasons of why developing countries are feeling the pinch is that developed countries have strong infrastructure. They have insurance coverage. They can afford higher medicines and higher cost

medicines, but poor countries can barely have that kind of arrangement. This is another irony. Multinationals generate over 80 percent of the revenue from sales from the developed markets. Almost the entire research is focused on the diseases that are done in the developed world. In 1998, \$70 billion was spent, out of which only \$3 million was dedicated to HIV and AIDS, only \$100 million to malaria. Between '75 and '96, in about 20 years, over 1200 new drugs were developed, out of which only 13 were developed to treat tropical diseases and 4 were the direct results of farmer. What did the World Bank have to say? It says what Dr. Barton in his phenomenal report has brought out that TRIPS enhances the value of patents. It provides more muscle to a developed country, and in the end, a developing nation remains a net loser. As a result, the U.S. benefits have gone across over \$19 billion annually. Royalties have increased from \$14 billion to \$22 billion. And there are good reasons to believe that TRIPS in its present form protects commercial investments and interests and not public interests. India, since the 70's, has been following process patenting the result that we have been able to bring about 25,000 small and big manufacturers producing about \$2.5 billion worth of drugs. Post January 2005, the majority of them will come under severe threat, and this is likely to lead to enormous demand and supply situations. Can India afford such a scenario? Can any developing country afford such a scenario? Compulsory license is but a small hope.

Why compulsory licensing? Child pneumonia kills millions of children each year, but the drug Erythromycin is priced so highly that a developing nation in Sahara, in the sub-Saharan areas, cannot simply afford it. India produces that drug at one-fifth of the cost, the generic version. But it cannot afford to export it due to the rigid patent laws. Compare this to the U.S. for example. Post 9/11, U.S. almost issued a compulsory license for Cipro. To date, U.S. has put exorbitant duty on the seal, on the U.S. seal, to protect its domestic market. In the 50's and 60's, the U.S. was the highest user of compulsory licenses. India has, to date, not used any. It is therefore of vital importance that developing countries must be allowed to come up with a pro-competitive solution for patented drugs that insure the availability of medicines at low cost. And there are black market concerns, of course, and this will happen at all times. Why? TRIPS grants 20 years patent protection for new drugs. That, in turn, delays inexpensive research in generic area. When medicines are very highly priced, cheaper substitutions will find their way into black market as perhaps one of the simplest. And while it is a nightmare for a manufacturer, it's a blessing in disguise for the consumer. In the context of a national emergency, therefore, it is the availability of the low priced drugs, and not the color of

the market, that plays a role. Try and see these poor countries and how they manage without insurance, buy those life saving drugs and the rock that they go through. It is definitely appreciated that R&D ["Research and Development"] should be paid for. But more often than not, eminencies rule the earth on the R&D, and would like to take their profit back very quickly. One has to see how much quickly. Differential pricing is one of the solutions that we think can come in. And it has been practiced in India in a big way. There are two methods, short and long. And both need to be worked simultaneously. In Canada, price controls are used to limit price increase of patented drugs. In India, differential pricing has been successfully used in areas of power supply, agriculture, and telecom. Since major income is generated from developed countries, developing countries should be allowed to produce life saving drugs using compulsory license with direct restriction on export to the developed world. I'll give an example. My company, Eckward Hoffman LaRoche's Indian Operations, inherited a drug called Bactrim. We sell it at one-fifth of the cost within India and do not export it. And to Washington, it doesn't make a difference because it's not their chief, but it saves quite a lot of people in our own country. Johnson & Johnson, on the other hand, sells within India, a drug at 10 times the cost, and it still survives. It's doing a roaring business. People who like brand and can afford quality of that brand, they go about it nevertheless.

R&D is another solution. We believe, you know, to pay to work class centers in countries that have intelligence capacity to deliver. To find already existing pricing instilled in public institutions in developing countries that have a successful track record, and whose performance could be bolstered with additional and directed funding. To create global knowledge network and with partnership between public and the private. But other than using spare and expensive capacity of large multinationals, it would be more productive to create drugs for the poor, using the capacity of the countries which are economically poor but intellectually rich, [getting] commitments to insure open access to a scientific database and commitments to insure that the benefits to public funding and research are available to all.

While I am talking about these issues, in most developing countries right now, there is a phenomenal amount of crisis because of TRIPS. What is going to happen in the end of the day? And while a developed nation—while a developed country can have too many areas to look around, a developing nation which is struggling to protect its people, trying to provide them with medical health care, is going to find it even more difficult. I'll give you a small example before I conclude. In India, we have

people talented who have produced phenomenal results. We have launched ASLVs⁵ and GSLVs,⁶ and jurisdictionally launched vehicles at virtually \$43 million, which is one-tenth of General Electric's research budget. Yet we produced this kind of result. [What] the government of India can at least do is to protect or provide health care. It is of importance to developing countries, therefore, to address these issues and have the developed nations address them in adamant seriousness. Thank you very much.

MR. BARTON: Thank you. Let's turn now to—

(CLAPPING)

MR. BARTON: To further exploration of the patent issues with Dr. Herwig von Morze.

DR. VON MORZE: I should say that I don't have a reservation about handouts in the third world so if anybody is interested and if my observations turn out to be unintelligible at least you will be able to read them. I would like to first explain my bias. Obviously, I worked for 27 years in the pharmaceutical industry, so I'm of the old fashioned belief that patents are really of the essence for the economic welfare of any nation. I'd like to address the issue as the first issue, the access of essential medicines in the developing world and the clash that is perceived and was addressed by the speakers before between access on the one hand and the need to innovate and the need to have patent protection [on the other].

First, a very basic question should be asked. Does this clash in reality exist? And I also want to differentiate. I don't think we can put developing countries all in one pot. I'd like to look at developing countries in the sub-Saharan, Africa, and then much more developed countries, India, Brazil, to a certain extent South Africa also. Amir Alteran of the Harvard Center for International Development has done a study. And he was investigating the question whether the patent system really prevents generic competition, keeps the prices high, and nobody gets treatment. And I need to say, I don't approach this issue in any way lightly. The old Romans got it right. It's "tour race aquitur," which means, you know, it's my problem, it's our problem, and it's the world's problem. So it's a very essential point. And I don't think that pharmaceutical companies look at that in a very light fashion—light-fashioned way.

Let's look at the sub-Saharan African countries, and the issue of AIDS there, which is sort of a critical issue there. There currently are 15

5. Advanced Satellite Launch Vehicle; this vehicle is a booster that places satellites into orbit.

6. Geosynchronous Satellite Launch Vehicle; this vehicle places satellites into orbit and was a part of the Indian Space Program.

AIDS drugs, retrovirals available, and the issue is, does the patent system, or do existing patents prevent that? No, because no patents exist in these countries for these—I mean, in free countries patents exist and they cover certain products but not in the 53 countries that are there. Then, obviously, the patent system, one would expect that in countries like Mozambique, since there are no patents, there would be adequate treatment. No, of course not. And I think my colleague before had said, and that's quite correct, there is no money. That's part of the problem. But beyond the issue of money, it's a question that the rich countries, who one would expect would donate more money, they don't really do very much. I mean, for example, the statistics prove that England does relatively, is relatively generous with \$147 million, but Germany only offers like \$3 million, Japan \$4 million. I mean, those are things that are really astounding considering that Bill Gates, himself, for the various the projects spends \$150 million, and that's a real . . . contrast that is somewhat frightening. Beyond money, what else prevents access to health care there? That's clearly that there is no health care system in place, a health care infrastructure, because it's not just—it's too simple to say it's the price of the drugs that prevents it. The price of the drug is one factor, but the other factor is you have to have educated physicians, you have to have hospitals. You have, even as simple as that, you have to have roads to get patients to hospital and to get patients to doctors. And that it is calculated that about for each drug or treatment in the AIDS area, you need about \$100 per patient per year. And the, what these countries can afford is in the \$10 or \$20 per patient per year at the maximum. And so that's, in other words, it's a fallacy to say that in these countries the patent system prevents access to medicines.

Now, let's look at India, Brazil, and South Africa. The situation is quite different there. Patents do exist with varying condition periods and varying enforceability. India just introduced new legislation in 2002, and after having some initial legislation in 1999, there is some adaptation to TRIPS. For example, the term was extended to 20 years, now. However, it began, it's a fallacy to say that these 20 years are at the disposal of the pharmaceutical company if one considers that the research and development takes about 10 to 12 years. Those are proven statistics that exist for the U.S., for Europe, and a number of countries. Therefore, a number of countries have recognized that the 20-year term is really misleading. It's at best 8 to 10 years. Now, India has in the patent law provided for other things that basically detract from patent enforceability, and compulsory licenses being one of them. Now, compulsory licenses is often focused on local manufacturer—that is, if you do not manufacturer locally, then compulsory licenses would be available for other parties.

Now, if—and there are many countries in which such a system would exist—Now, if you tried to, as a pharmaceutical company, to manufacture in all those countries, the price of pharmaceuticals would skyrocket. So that is not really a proper solution. Now, we have seen that in India there was up to—again, the 2002 law was a relatively strong law on copyrights. And that helped fostering basically the really strong development of computer science in India, in addition to excellent schools. Now, India has in the new law, abolished the protection for this, and I'm just wondering what will happen to the industry. But clearly the patent system or the copyright system has helped their developing, the product, the industry.

Just a minute on Brazil and then I am closing. There were reports that Brazil was using the compulsory license mechanism to make products available, but it is not true. What the pharmaceutical companies have done, and they are willing to do, is to supply drugs at the generic prices, which has happened in the case of Brazil. Eighty percent of the needs of the AIDS' patients was supplied by the pharmaceutical industry at very low prices, and 20 percent was supplemented based on local manufacturers because there was no patents.

I just want to give you one last example before I close. There are efforts, for example, by Pfizer to make drugs available—I think it's Citromax for the River Blindness in Africa, at very low prices, and that's a project that has been very successful. In summary, I don't think the patent system is the culprit. That's my [opinion].

MR. BARTON: Thank you very much. Our final two presentations are more about how to do it. Let me start with Vernon Winters, a partner in Weil, Gotsshal & Manges.

MR. WINTERS: Thanks very much. I wanted to talk today a bit about, you know, we're here at a conference talking about patentability generally and policy issues. I wanted to bring a real world focus to that and talk about what it means to biotechnology companies to be able to secure a patent. And I want to do that two ways. I want to take sort of a historical look back and then a cautionary look forward. And the look back is going to concern patents on gene sequences. And we all today take biotechnology advances pretty much for granted. We read about them in the general press. It's likely that people that you know or perhaps people in this room have benefited from advances in biotechnology. It could have easily tipped the other way. In the early 1980's, really at the birth of the industry, there was a lot of concern both within the scientific community itself and the general public at large, about what it meant to be able to take gene sequences from one living organism and put them into another to make pretty much—generally the talk was about recombinant proteins. What did that mean?

There were famous monsters in the sewers debates at Harvard about the possibility of recombinantly engineered E. Coli could leave the laboratory and create crocodiles in the sewers. I'm being a little facetious. There was a lot of concern in both, as I said in both the scientific community and the general community. And so what the scientific community did was hold, some of you probably know about this, the famous Asilomar Conference,⁷ where people, the scientific community, looked at the ethics, and the scientific risks of being able to take gene sequences and use them to program other organisms to produce proteins and called a moratorium on all that work. There were also questions at that point about whether or not gene sequences were patentable. That was far from clear under the U.S. patent laws. How did that resolve? As we know, the scientific community, working with itself with a lot of inputs from legislative people from lawyers, from bioethists, which is, you know, a well accepted field now was just at its infancy then, concluded that the risks were acceptable. And in 1980, the U.S. Supreme Court stepped in and decided in the *Diamond v. Chakrabarty*⁸ case that living things were patentable, and that decision is generally pointed to as the legal event that enabled companies to take out patents on gene sequences.

So what happened since then? I would say it's largely an unqualified success, at least here in the United States. The FDA has approved more than 130 biotechnology drugs and vaccines, and those have helped more than 350 million people worldwide. Here in the U.S., the biotechnology outspends on a relative basis, other industries on R&D by sometimes factors of two and three, and in 2001 alone, spent nearly \$16 billion on research and development. And in 1999, just within the U.S., the biotechnology industry generated \$47 billion in revenues, created 440,000 jobs, spent \$11 billion in research and development, and \$11 billion in tax revenues. Now, could any of that have happened without patent protection? It's sort of hard to know, it's hard to create an alternate universe and run that experiment. But I don't know many people who credibly advanced an argument that it could have. If you talk with executives at biotech companies, with researchers, with economists, the phrase that recurs over and over and over again, is 'patents are the life blood of the biotech industry.' You can find that quote from the CEO's of Biogenentec, Amgen, all the major companies.

And, okay, why do patents necessarily enable biotech companies to produce these drugs upon which we've all come to rely? Because the risk

7. For more information, see http://amwancal.org/Asilomar_conf.htm.

8. 447 U.S. 303 (1980).

reward ratio to try to produce a new biotech drug is very high. It's been estimated—there's a center at Tuft's University that studies this industry pretty closely. The recent estimates are that it takes \$802 million and 10 to 15 years to go from start through FDA approval to get that first drug into a patient. Biopharmaceutical products have enormous failure rates. It's been estimated that for every 5,000 medicines tested on average only five reach clinical trials. And the FDA approves of those five only one for patient use.

So that's the look back and here's the sort of cautionary look forward. We're at the preface here in this country of another potential biotech revolution, and I'm talking about stem cell technology. Probably people in this room are aware of what's been written about its promise. And you can only call it that. It's absolutely in its infancy. But there is debate now about whether or not stem cells ought to be patentable, whether or not we ought to be investing in it here in this country. And the real world effect of those sorts of impediments to patentability and research are that that key technology is now going elsewhere. So, for example, Singapore has recently invested nearly \$2 billion in infrastructure and personnel to try to make it one of the key stem cell centers in the world. Roger Peterson, one of the leading stem cell researchers here in the U.S., recently moved his laboratory over to the UK because of the climate here. And I don't have an answer. I'm not suggesting an answer here. But by concluding that certain technology should be beyond the reach of patents or that certain technology should be beyond the reach of what we should be investing in, we're making real world choices about where those developments are going to occur, and in my judgment, if they're going to occur. Thank you.

MR. BARTON: Thank you. And our last panelist is Don Francis, President and co-founder of Vaxgen.

MR. FRANCIS: Thank you, John. I would actually like to get down to the nitty gritty of doing and using our experience with trying to make a company initially, solely on the pursuit of an AIDS vaccine to show the examples you have to deal with both intellectual property and the challenges of the whole world process. I think the issue for biotechnology is here we have the possibility in modern biotechnology to make vaccines for dangerous agents, like HIV, that can indeed approach the whole world. So from the beginning there we're taking modern biotechnology and thinking about vaccines for the entire world from the founding of our company onwards. And a lot of that dealt with the issue of what side this private public partnership can get the job done. And I, as someone who was in the government for 21 years, realized that it was really only industry that could do it, and so retired and tried to see if you could do it from industry. Well, industry has a hard time, too, actually in the vaccine business. And

I'll get to that in a bit. But by and large vaccines don't compete very well in a structure that we have where, as John mentioned, all the profit comes from the industrialized world, where as by and large a lot of these diseases are in the less developed parts of the world. But HIV is unique, unique in several ways. One, it's unique in that here, we drove the founding of this company, understanding that there was a high incidence of the disease in the industrialized world and a need for a vaccine, and there was huge incidence in the less developed parts of the world, and there should be some way to balance that. And so; as was mentioned, you have to talk about hundreds of millions of dollars. We spun off of Genentec, Genentec put about \$50 million into this vaccine and we have raised \$130 million just for the development and another \$100 million for manufacture. So, you're getting into the hundreds of millions of dollars, and you don't know if a vaccine works. And indeed we've had our first trial that has been a relative failure. We still have some clues that may lead us onto a vaccine, but another \$100's of million are going to be required to actually move that forward. What's interesting is I've seen other companies deal with AIDS vaccines in a quote that I will not give a name to, but there's only a few companies working on AIDS vaccines in a large sense around the world, and one of the largest companies that's working on it, a very high level individual in that company recently told me that the whole staff of the company just prays the vaccine is not successful because of the tiger by the tail issue one will have with an AIDS vaccine.

So, in an opportunity costs situation, the reason that we spun Vaxgen out of Genentec in the first place was that within a pharmaceutical company, vaccines don't compete. If you think—if I think about this back in the early days of AIDS and the discovery of the virus, I thought a vaccine would be available far before I thought an antiviral would be available, because antivirals are really tough, especially with little agents like viruses, where there aren't very many targets. And yet, there's a dozen or more antivirals out there on the market and there's not one vaccine. And that's really an issue of how much resource has been put in. That was a very hard challenge to get antivirals. And so, within the—looking at the public [and] private side of this, the public side can't do it and the private side is not very interested in doing it. So you have a difficult issue, that frankly is not centered around intellectual property. We have huge intellectual property that protects us should we have a vaccine, but an awful lot of that is know how, and this is a tough product to make, and it's just not going to be stolen here and there. The issues that I see if we have a successful vaccine ultimately, is how we're going to take a relatively expensive vaccine—It really is in the dollar sense, not in the hundreds of

dollar sense, but in vaccines that's about a log higher than is usually expected—and get that delivered, and how to do it inexpensively and get the return on the investment. But I think that can be dealt with, in John's words, at tiered pricing. With an AIDS vaccine, I still think there is a market, but again, relative to other products, there is not a market and therefore, there aren't too many companies interested in it.

Let me quickly deal with some of the reality where the tire meets the road issues, just for this, and that is—looking at the early parts of the studies [to understand] what we were confronted with. First of all, it's hard to do in the developing world, because you needed a really a considerable infrastructure to have a well-managed, large-scaled trial of thousands of people. And fortunately, the World Health Organizations set up of a variety of places, only one of which was actually functioning by the time we started out in Bangkok, Thailand. They really had the capability, with a certain amount of training and FDA-type regulatory oversight, to actually do a trial very effectively. But it is a challenge to go to the third world and do these large trials. And since this virus seems to vary in different parts of the world, you really have to design your vaccine for that part of the world and do the studies there.

Next, what was interesting in a legal sense was the regulatory/ethical overview of the trials, in that there are different rules in different places. And so when we were combining U.S. rules and Thai rules, you end up having double duty with regulatory approval. And indeed the Thai trial was supposed to start before the North American European trial and it started later. Since this part of the world is very accustomed to the regulatory approval of research, that part of the world isn't necessarily, and when you go through setting up new committees, and going through the committees for the first time, it was a bit of a challenge.

The other thing that was interesting in a legal sense is the desire for the developing world to have a piece of the action for your vaccine and have a promise of reduced pricing, etc. before you even know whether you have a product, and how do you do that with a start-up company that doesn't know what the outcome is? And how can you deal with that issue when you don't know what the prices, what the realities are, except giving nice words? And fortunately, the countries we've worked with have been able to be satisfied with that.

And then finally is the issue of actual supply of the product when you've finished, not only the price of it, but how you're going to deal with the priorities. Think about a small company like ours and we do have a successful product, that is equally successful in the developing country versus the industrialized world, and the profits that one can get from the

industrialized world would just be massive, especially when your capacity is limited for manufacturing as it is early on. You'll be in a very tight situation with a huge public health need in your less return side, and your high return side having less public health need but getting the return to get your company to survive.

Finally, let me just end with the issue of why we have this discordant situation fee between vaccines and therapies and the opportunity cost conflict that you have at Genentec or anywhere else. And it's really a line of social value. Frankly, our societies are not—world societies are not mature enough to value prevention in general, and therefore, even though everyone gives very nice lip service to something like an AIDS vaccine, the immense need that anyone in this room would come up within five minutes of a review of having an AIDS vaccine, it does not compete and so you have no vaccine for AIDS and a dozen therapies out there that are equally hard technologically to make. So the lack of social value leads to a lack of industry interest. And it's not a issue of legal or intellectual property. It's really just a basic issue of economics. As long as the world does not value such things as prevention and long-term cost reduction, we just won't have the biotechnology industry getting into the field even though the power is immense now. Thank you.

MR. BARTON: Terrific. Thank you. And thank all five of you for getting us off to a good start. I'm going to exercise the moderator's prerogative of asking a first question or two. And let me aim my first question at Mr. Winters, and at anybody else who would like to respond to it.

Pharmaceuticals are the highest growing component of health care costs in the United States. Pharmaceutical prices are increasing more rapidly than any other product. A large percentage of this is being placed in the form of price tensions and health care systems and HMO's and on employers. The fair chunk of it is being bought by the government. We're considering a program of government purchase of pharmaceuticals for the aged. I cannot imagine that that will not be soon followed by price controls. Is the pattern that you've described going to last? How are we going to resolve this increasing tension between prices and a system which has served us wonderfully, of course, a system based on patents? What do you see as the future? And I'd love to hear comments from any others as well.

MR. WINTERS: Anybody else want to go first because that is a big question?

(LAUGHTER)

MR. WINTERS: I don't know the answer. I don't have an answer necessarily. I mean, there are some immutable facts here. One is that, and

we've hear from first hand that this is true, that trying to create these medicines is a very high risk, huge expense reward. And that is why, frankly, countries in the developed world are the leaders in creating them. It's because we're the ones who have the capital to do the investment, and part of the reason we have the capital to do that investment in the biotech context is because this country is the leading biotech country in the world. And the successes we had early on are the things that are funding the success now, and this institution is not exempt from that. As you probably know the Cohen-Boyer Patent,⁹ one the great early biotech patents, I think the published figures are that that contributed something like \$200 million to Stanford. I might have that wrong, but I think that's right.

MR. BARTON: I think it's 150 or roughly. First of all, you're absolutely right. It's a very difficult question. Is it a question that is real or am I having a misperception seeing this as an important issue?

MR. WINTERS: No, that's absolutely right. It's a valid question. It's, in my judgment, the biopharmaceutical industry has badly managed their response to that question on a public relations front, on an economic front. I'd love to hear what some of my colleagues think the answers might be.

MR. MAURER: I don't have an answer, but certainly when I sit around a panel like this with other biotech physicians and executives, it's interesting that our focus is worldwide and so we deal with international issues. Most of them say, we're only interested in the U.S. market, maybe Europe, because that's the only place we get our return. And they haven't even thought about moving it on to the less profitable side because when you have these, with that \$800 million per drug develop, I think that is correct, because five of them fail. So if ours is correct then ours is a \$200 million process to find out whether it works or not. And you have to spend a billion dollars to get one success. So, 800 is not far off. But you need a lot of money. I saw the other day about—remember Chryslers' bailout by the U.S. Government where they put that money into a redesign of a new product, which was the minivan, and that was only a few hundred million dollars, which is about what we pay for one drug development, and look what that did. So, in a relative sense, this is a lot of money, and without a high return, you're not going to get that kind of investment. Now, can you do it cheaper? Will you get the same returns? Who knows if it's going to continue to be this expensive. But a lot of the expense comes in ultimately the phase three trials, which aren't going to change very much. You have large numbers of individuals. It takes hundreds of million dollars to get the

9. U.S. Patent No. 4,237,224 (issued Dec. 2, 1980).

final results of the study. Those aren't going to change very much. So maybe the research can be done cheaper but, seems like with regular—the way we do these trials is so compulsive and so it may be overdone, and it is expensive.

MR. SIKKA: But if I may add, there are countries which are economically poor but intellectually very rich. I would—in India and the kind of progress India has made within and created virtually not a phenomenal amount of results out of nothing. If more focus is given to these countries, perhaps they'll be able to come out with phenomenal solutions at low costs. There has to be a side-by-side balance. Let there be competition. Let our intellectually rich country produce something with a limited number of funds, which is not happening right now.

DR. VON MORZE: Perhaps if I could comment on the issue, as far as the developing countries are concerned. Of course, one cannot even put the United States and Europe in one pot because you have much more price control in Europe and governmental price control. And let me just give you one example that, of course, pharmaceutical companies are somewhat frustrated about because, of course, it affects immediately the return on investment. For example, it may take as long, you may get your product approved, but to get on the health reimbursement scheme, it may take as long as two years, because the price that you are trying to get based on the research investment does not suit the health authorities. And, you know, that's why it's a very difficult question but it's even multifaceted in the developing world. But, you know, I would imagine that there would be eventually, although companies wouldn't like it, there would be some sort of price control even in the United States eventually. You know, that's something that's probably, I mean to a certain extent, it's happening that you have certain lists in hospitals that you need to get on these lists, and many products won't make it on those lists because they're too expensive. And there are maybe alternatives available, therapeutic alternatives available.

MR. WINTERS: To some extent, the future's already here, because the other thing that brings down prices is buying power on the buyer's side. And monopsony is very large in the United States and as soon as you get outside the United States, the price differentials between drugs here and in Europe are often 50 percent or more. And we talked about incentives this morning where you go to a Canadian policy conference, they're quite honest about saying, look we export very little innovation to the rest of the world. We import a lot of drugs and we understand our best interest. So we may not have so far to fall to John's world because there are a lot of market imperfections, even in the states, which means that the price of drugs is sort

of set by arm wrestling rather than by a blind impartial market.

MR. BARTON: Let me hit you with one more hard question and then ask you to be the starting person. You suggested, you know we have to find a subsidy to hide things in a way that's hidden from Congress. And I'm not sure we have to hide it from Congress, but I agree completely. I mean, there will need to be a subsidy, and the question is, do you in essence pay it through the international development community, through international health systems, through pharmaceutical companies, with differential pricing, asking them to give up possible economic grants in developing countries? Clearly the question is, where do you find that subsidy? But I want to ask—and I don't know the answer to that? It's a political question. But I wanted to ask sort of a more practical question, given the group we have here in particular. Is it better to put that subsidy at the front end in terms of what is a moving NIH or something like NIH, further forward in the development process, or is it better to put it backend, in terms of saying, if you private sector come up with something, we'll make sure that we pay you a price that's high enough to cover your R&D costs. And I guess I'd like to hear some thoughts on that before we open it up?

MR. MAURER: I guess my two thoughts about that is that there's a very powerful example from the post war. We've just talked about vaccines and that they're everybody's poor relation. We do things differently in the postwar. It was largely people like March of Dimes and also to a smaller extent the federal government in those days, March of Dimes was actually bigger than the federal government in vaccines, and it was developed publicly. And then it was produced by the companies without intellectual property rights but with sort of oligopoly advantages, that I know how to make the stuff and nobody else does, so you can get some price out of that even without a patent. But that was a world where basically, you turned the National Labs loose on it in modern language. And I had talked to people in National Labs over the last week or so about this question and they sort of say, boy, wouldn't that be a great thing that we could be in that business? I think the real question about the advantages of IP is that we'll be more expensive in dollar terms because you have this monopoly pricing. And the question is, will we drill more dry holes than in a world where the government drills the dry holes? In other words, is there something about IP that elicits information that isn't public, that we need to avoid this dry hole, and that the private sector will avoid that better? Because both sectors will drill dry holes. The question is, are you going to get into a pathology where the government guy needs to go to work every day and so he doesn't quite say, you know, I think this will be a dry hole, but hey, I'm going to drill it anyway for a couple of years? I've got grant money. Those are the

kinds of things we need to worry about in incentives. But the absolute cheapest way to do this is to hire it done directly without the IP incentive. I think that's pretty clear. The question is will we end up with these information pathologies that the private sector does it better?

One last thing, if you look at how the National Labs were born, with this tremendous inventiveness in the Second World War, where people came out of academia, they had a great cause, they participated in it. I'm not of that generation, but I can say when I talk to National Labs people about a malaria vaccine, their eyes light up the same way. I mean, I think they want to roll up their sleeves and do this. This could be the great good thing of our generation.

MR. WINTERS: Having been on both sides of both the government and the private sector, I think it's really an issue of people and the measure of outcome. And there is no organization right now in the government in this by and large that develops. As you point out, the dry hole for an act of academic is not to bad. That is if you, you actually—if your output is publishing manuscripts then dry holes or wet holes are expected to be more important. You might get a better journal but you still get a number of manuscripts compared to a product out. It's a very different philosophy. And we've done both in AIDS vaccine, worked closely with the government, abandoned working the government, probably back in working with the government. It is not as easy, as long as the government forces, really you're coming out of the National Institutes of Health which are research organizations, . . . not product development organizations. It's very different from the March of Dimes, which got a bunch of academic folks together and said, let's make a vaccine. And it was make a vaccine. It was not make a manuscript. And it depends on how you measure the output and currently it's not terribly effective, at least not in the vaccine field, that I see.

DR. VON MORZE: There's one comment that, you know, about dry holes is one aspect of it. But the problem that also the government centered development would have is eventually they will have to contract with pharmaceutical companies because the marketing, the development of the market, and exploitation on the market side, I don't think this could work through the government. I mean, that has to be done through the industry.

MR. WINTERS: I would like to make one more point. Things have really changed. It depends on what the government's priority is. You would think the government priority would be very high in developing an AIDS vaccine, and it was not. You can read the book "Big Shot"¹⁰ if you want to

10. PATRICIA THOMAS, *BIG SHOT: PASSION, POLITICS, AND THE STRUGGLE FOR AN AIDS*

get the [gist] on the AIDS vaccine; there was a very good review of it. But recently—we're the U.S. contractor for the anthrax vaccine, and when the government wants to make an end, will make a vaccine and develop a vaccine. Totally different. And, if we are successful it will probably be a total record in terms of making a vaccine with speed and resources. So if they want to develop something, in a militaristic fashion—you know, how five people died of anthrax, and boy, the pressure to make an anthrax vaccine [became] huge. That's about three and a half seconds of people in AIDS, but, per day, every three seconds. But it still is a—if the government really wants to do something and do it properly, and you've got right now former military medical general saying, you make it, "bub" and it's functioning and it's fascinating. But it's also a small group of people doing it. It's not a big thing yet to them. They meet every week and beat us up and we beat them up and get it done. So it's very interesting how you can get it done, much like the March of Dimes, but the conflict and the politics of, yes, it will work or no, it will work with something like AIDS and academia was a disaster. But the same thing happened with polio where Jonas Salk said he had a vaccine, Albert Sable said, no you don't, and finally the March of Dimes said we'll fund both of you, and go for it. And thank goodness it did.

DR. VON MORZE: That would be also a different scenario because there would be immediate market acceptance. It's not something that you have to promote and go through sophistication.

MR. BARTON: Let me open it up for questions from the [audience], I noticed that there were a couple of hands earlier. Sure.

AUDIENCE: This is more of an international angle of it. To what extent has the various infrastructures [talked] to each other so that at least we avoid the duplication effort and the eventual transfer of these costs to the consumer? I'm having, regardless of the fact that it has been said that in the area of AIDS there are various problems that strains, that they call it, there are various strains. So maybe one is working on these strains and they don't have the results that many in sub-Saharan Africa may want. I mean those are two related issues. Thank you.

MR. FRANCIS: Certainly a cartoon that the AIDS drug is going to have spillovers if we make one for the United States that it will have spillovers to sub-Saharan Africa. They are different. So these are sort of artificial distinctions to some extent. I do think, and there are people a lot better qualified than me on the panel, that there will be considerable learning. If you can make one for the West, you'll probably learn an awful

lot about where to drill the next hole when you do the sub-Saharan version.

MR. MAURER: I think there is lots of communication but the amount of money going in it is actually, it is trivial. I—if you look at the balance of sub-Saharan Africa as far as need for an AIDS vaccine versus the United States and Europe, the balance is absolutely skewed. But actually how much work is being done for an African vaccine, there is a little bit, but it is trivial compared to the economic and personal impact. It's terribly out of balance. And I think prevention tends to be out of balance for therapy as I mentioned earlier. But this is an example without compare.

AUDIENCE: INAUDIBLE

MR. BARTON: Wait a moment so we can get the loud speaker, please.

AUDIENCE: John, you started out with the first question with pharmaceuticals being the fastest growing segment of health care costs. That's the costs side of it, but can you also consider the benefit side of it? Because of the pharmaceuticals we've got better quality of life that increased life span and quality. So does the cost justify the benefits?

MR. BARTON: I think the question is evaluating how good the pharmaceuticals that come out are, and how they compare with alternate things that we might be developing? I think there is certainly a set of risks associated in part with what kinds of products have the best market. And I think I'd appreciate other thoughts on this. I have my best market for a product that people take every day as opposed to a product that they take once in their life. There are set of risks for that type, which, of course, cuts against preventive therapies. There is also a set of risks associated with the tort liability system, which says, something which you give to somebody getting old involves much less potential liability risks than something that you give to somebody who's a child, or worst of all a pregnant woman. Therefore, I think we see a significant set of legal system based skewing in the focus of research. And I think I want to know the answer to that better than I actually do, about how much skewing actually occurs. But those would be my hypotheses and my suspicions.

MR. BARTON: Other people?

AUDIENCE: My question is for Mr. Sikka. To what extent—you mentioned that many people are unable to afford drugs in developing countries. To what extent is that among lay people viewed as the fault of the U.S. or something being imposed on them by the U.S. or do they blame their own governments? And then if so, do those governments sort of try to pass the buck and say well this is because of the international property regime put onto us by the U.S? Essentially my question is, how much sort of ill will are we gathering up as this continues among lay people who

haven't studied TRIPS, etc.?

MR. SIKKA: Well, there's no ill will per se, if that is your focus. Second, like India, we, in the 80's, we were denied super computers. We somehow managed about \$35 to \$40 million and produced a super computer product within three years, and it matches the best. We are in this no-win situation today. When I was in Geneva last December, one of the ambassadors of the developing countries came out after the U.S. blocked the TRIPS, and he said we are all in a comma. We still believe we are just at a comma. It's a matter of how you take a pause now and then go on to write sentences and chapters and paragraphs. There's always a way to go about it. There's no ill will. For sure, developing countries will always come up with something. It may not be the best, but we will—they'll be able to meet their requirements.

MR. MAURER: But for you who have not been to the developing world looking at health care, and it's not uncommon for a country in the less developed countries to have what three, four, five, six, eight dollars per year per person for health care, whereas we're running what, about \$4,000 now in the United States. So when you talk about new biotech drugs that are expensive to develop, what was described in the clever ingenuity of India no doubt, to make drugs there, not to mention super computers. But there's not the economic hit necessarily to be able to purchase them once you get them out.

MR. SIKKA: Just to add to it, say Kenya spends about \$20 odd per year on health care. Norway spends over \$2,000 per head. I'm perhaps mistaken it's much more. You cannot overnight make out a law and then compare Kenya versus Norway. I know there has to be a buffer zone and if we are not going to allow that buffer zone to take shape, initially there will be a little bit and things will come out. There's always a nature of concern.

AUDIENCE: We were talking about the high cost of developing medicines, something like \$800 million to bring a drug to market, and we talked about the reason that it's so because the costs associated with trials so high, probably because our government is so risk adverse in bringing those new drugs to market. Is it possible to—is it possible for companies to run trials in developing countries where clearly the cost of running the trial would be much, much lower, for marketing the drug in that country? And, if so, does that represent a reasonable strategy to bring new medicines to developing countries first, at a far cheaper price, while it's struggling through the ten years of regulatory approval in the United States—I'd just like to hear a comment to that.

MR. MAURER: We're doing our first retrial in Thailand but in terms of the return, you're going to get a lot less, but we're doing this for not only

making worldwide vaccine development and taking different strains where you have to do it there. There's a lot of work done in the developing world, but is that the market that's going to drive this multimillion-dollar return? As I've mentioned before, the panels I've sat on with other folks say that we're interested in the United States and that's all. At \$4,000 a year per person, you can see why. So you can do the trials there, yeah, but then you really have an ethical situation. You do the trial there and then not supply the drug?

DR. VON MORZE: Perhaps the other point I want to make is this. As I mentioned in my remarks, it's very difficult to do clinical trials in some of the developing countries, because, I mean, the infrastructure is not set up. You will be probably the first trial ever done in a country where the need for this essential medicine exists. But what I can say is this, I know, having worked in a pharmaceutical companies and still in contact with pharmaceutical companies, it is happening to a large extent, for example, with countries in the former Eastern Block countries, you know, Slovakia, the Czech Republic, Hungary, Poland, because—and even Russia. There are actually quite experienced physicians there to run clinical trials at a substantially reduced cost. So it's—and that is happening. But the key is also, you cannot have data that you could not submit to the FDA. You have to have, you know, the same standards [so] that these data are useable also for FDA or Europe. But this is happening, you know.

MR. BARTON: May I ask a couple of follow up questions to that? First of all, I know there's an international conference on harmonization, which is at the very—I mean, obviously it's not harmonizing product approval standards, but is at the very least seeking to design things so that I can take a study in one country and submit it as part of my package in another country. Is that really working and is that going to be useful, you know, with the possibilities of doing studies in Thailand and in Eastern Europe?

DR. VON MORZE: I really lack the expertise to answer the question.

MR. MAURER: Doing high quality studies, it's just—it can be done anywhere in the world if you have the right, as you mentioned, having the right researchers. There are talented people everywhere. And even the, in the poorest of sub-Saharan Africa, I'm sure we can find, and indeed are talking to, people who can do outstanding research. Now, some of the issues for therapeutic drugs and the diagnostics and such, you need, you have to put that all in place. It can be done. There's no doubt about it. And the harmonization, what is happening is that Europe and FDA are setting these standards. And there—let me just back up. The reason that these

standards are so high is because the assumption is the pharmaceutical researchers are cheating. Because you have huge economic advantages to cheat on your studies to make them look good. And so the rigor that you have to do to them that insures that when the FDA comes in they can drill all the way down to the European, or whatever authority, comes down, they can drill all the way down into your data base and see that you did not cheat, is much more expensive research than just doing assumed honest research. I think it's reasonable because I think people will cheat to because the economic advantage is high . . . , but I think those standards can be done anywhere in the world.

AUDIENCE: I wanted to ask you about the cost benefit analysis that we structure in the United States, where both the profits that a firm obtains through its IP and the negative aspects of risk, primarily through litigation that we've seen since 1980, so that very formidable pharmaceutical firms that have helped people for over a century suddenly go out of business when a single drug has a negative outcome. And contrast that to the developing world, for instance in India, where they still use chloramphenicol¹¹ because the drug is a very useful drug. It's very important. It saves lives. But we can no longer value the saving of a life individually versus the group. How do you respond to that?

MR. MAURER: Well, I hate to speak against litigation in these hallowed halls. And I think litigation does drive some honesty. It can obviously go to the extreme, but it does drive one to, if one is doing bad things, at least, to cover it up better. But—

(LAUGHTER)

MR. MAURER: But there are some things unique to the vaccine industry. We cannot survive in the vaccine industry with just wild litigation because if you immunize everyone in this room, somebody will get sick, unfortunately, in the coming months, and if they blame it on the vaccine, they'll then sue you. And that's been a horrible, and that drove the vaccine industry essentially out of business, almost and totally out of business in the United States down to just a handful. And we have an expert on this next to us. But it's a real—that kind of litigation—for anything you give to healthy young people is a problem. Because one, they're young and they'll live a long time and plus some of them are not going to be healthy no

11. Chloramphenicol is a toxic antibiotic which may cause serious side effects. These include blood dyscrasias such as aplastic anemia, hypoplastic anemia, thrombocytopenia and granulocytopenia. Headache, mild depression, mental confusion and delirium have also been described in patients receiving chloramphenicol. Chloramphenicol is rarely used, and its purpose is to treat typhoid fever, some forms of meningitis, spotted fever and typhus. See <http://www.healthcentral.com/mhc/top/001740.cfm>.

matter what you do. We have, we've given our vaccine to about 3,000 people and we've had somewhere in the neighborhood of 50 deaths in that period of time. Now luckily we have a vaccine and placebo trial so that you can look at the number of deaths in the vaccine group and the placebo group and see there's no interest, I mean, there's no increase. And a lot of these are driving their motorcycle into hard objects but you could say that the vaccine made you dizzy and therefore you drove your motorcycle into a hard object. And it can be terribly expensive to try to defend. And the sad thing is, there are little kids who get autism or whatever else, and it's driven the vaccine industry crazy with litigation. So now we have a system to deal with that and I think it's doing relatively well. But we could not, literally could not, even think about marketing an AIDS vaccine without some sort of intermediate steps to protect against random litigation. Now, not—now, negligent litigation, I think that it's perfectly appropriate. But the non-negligent liability associated with giving healthy people things, birth control pills, anything you give to healthy people, some of them are going to become unhealthy and you're going to get blamed for it.

MR. BARTON: Did you want to comment on the safety approval process in India and also whether you have litigation worries there?

MR. SIKKA: The—most of the world outside does not understand quite clearly what India goes through. One billion people, 80 percent of them unable to afford [insurance and there is] no kind of insurance infrastructure. And let's talk about the approval systems that we have there. Anything and everything was going on and sometimes we believe that it still goes on. But over a period, the structure has improved. We've not only, engineers are working day and night and coming out intelligent companies which are now producing results. Pharmaceutical companies themselves are fighting tooth and nail and making sure that if somebody thoughts lose and stuff, they are taken to task. We are personally fighting an Amgen case in India, on a matter, and taking on a major company, pharmaceutical company, and we believe that it was not approved by the drug authorities in the manner in which should have been. So those systems are taking shape at a rapid pace. There are not much to satisfaction and it will take us time to do that. They are coming of age as of now.

AUDIENCE: Any one of you that can answer this. I'm interested in knowing a little bit about the role of generic drug companies in the United States and I was wondering if any of you can speak to generic companies' success or perhaps failure in bringing low cost drugs to market and perhaps to developing countries.

MR. BARTON: Let me start with that one and then give my colleagues a chance to respond. Sort of by definition the generic industry

doesn't bring new products to market. In other words, the fundamental definition of generic—the fundamental concept of the Hatch Waxman Act,¹² and I'm interested and wondering whether it's under political tension as well. But the fundamental concept of the Hatch Waxman Act is we have sort of a brand-name, research based pharmaceutical industry, that has patent protection, and that at some point, when the patent ends, and there's all kinds of legal games and complications about exactly when you lose your exclusivity, infinitely complex statutory interpretation problems. But when you get past that point, then generic competition can enter upon showing that the product is biologically equivalent to the product that is already on the market rather than upon showing the enormous zillion dollar tests that are needed to show that the product is effective. Therefore, the generic industry is available as a way to produce existing products. And one of the real issues in this global balance is the extent to which generic companies, traditionally in India, should be competing with brand name pharmaceutical companies, in let us say, South Africa, or something of that type. That's one of the points of political tension. And in this sense, there is an Indian generic industry which is based on the fact that patents—product patents haven't been applicable in India. Those product patents will become applicable in India in 2005. And at that point, what happens to Indian generic industry is a very interesting question, and I'd love to hear some thoughts on it. But I can look to those people to provide me cheap, competitive priced copies of existing drugs under a bargain in which we reward the company that brings the product to market, but then at some point, let the price drop through the generic competition. And that's the precise bargain of the Hatch Waxman Act of what, 1984? '82?

MR. MAURER: 1984. As subsequently amended many times.

MR. BARTON: And I guess I'd like a little bit more from my colleagues on that.

AUDIENCE: Will you speak into a microphone, please?

DR. VON MORZE: I'm sorry. Yes. The problem is not only that there are no new products, but there's such a huge price differential between the less generic price—yes, even the Canadian generic price, which is much lower, that would not really be helpful for the developing countries because it's just not, you know, only a company like India or other countries could produce at a much lower price, the generic product. But definitely, it's not happening in Canada. It's very difficult to imagine.

MR. SIKKA: Let me add some interesting scenario to this. Over 80

12. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) ["Hatch Waxman Act"].

percent of the drugs today are likely to be in the next couple of years going to be off patent. Of late, in the past three or four years, Indian companies have started coming into America and started to enter into the generic business. When President Clinton visited India, we, my company, was invited to make a special presentation to him, and we explained to him how American medicine bill can be brought down by 10 fold, 10 times. And we gave a rationale behind it. We explained it to him that without compromising on anything, quality and stuff, the total bill can be brought down. The problem is that too many guys know about it. They're going away. It will take time, and this is perhaps one of the fears of these multinationals, that they fear we're going to come in and barge into their market. It's not really that. It is happening at a slow pace, and perhaps the next ten years are going to be very interesting. The aim of the developing countries is to bring down the prices down because that's their own need. And generic does not cost much. We're insisting on the developing countries must be allowed to come up with pro-competitive solutions and that is where the solution lies.

MR. WINTERS: Some of the technology, I don't know, if you took the small molecule market, not the biotech stuff, took the small molecule market, a huge amount of the drugs that we use here, at least the beginning materials for them, if not the final product, are made outside the United States now. Truly the drug industry is a global industry no matter how you look at it.

MR. BARTON: It's not in India, if I understand it.

MR. WINTERS: Yeah, India and Singapore, and China.

DR. VON MORZE: China, yeah.

MR. SIKKA: Brazil.

MR. WINTERS: Brazil.

MR. BARTON: Then we'll give you the next chance so you don't have to run.

AUDIENCE: I was wondering if the panel could comment on the proper role of TRIPS compulsory licensing, and if Mr. Sikka could comment on what he perceives that the limits will oppose on India in 2005, and maybe even India's—is India being a strong generic industry, it's role in sort of compulsory licensing exporting necessary drugs to the least developing countries.

MR. SIKKA: Well, if Professor Barton allows me, I'll take it in a lighter vein and we've become a little too serious. In our country there is a fear about TRIPS. Perhaps, perhaps I can send a message. There is a tribe in India which is known for its ferocity. They are very aggressive. They remain a part of our Northern Block. And they do not deal with the major

force that allowed, they kept Moguls at bay. At one point they occupied a particular land and said that it belongs to them. And government realized that there is no point in pushing them. They'll not listen to anything. And they said, okay this land is yours. You have to come up with two crops. That night they all celebrated and took a lot of liquor and decided the first crop would be sugar cane. One old man from this warrior tribe got up and said, if for the neighboring village picks up and steals your crop what will happen? They said okay, let's sort out the neighbor first. So they went lock, stock and barrel and hammered the neighbor's house, and the neighbors try to ask what have we done? Dare you steal our sugar cane?

(LAUGHTER)

MR. SIKKA: TRIPS fear of developed countries, I think, is unfounded. Let it come into place. There's miles to go still.

MR. FRANCIS: I think it may be even a little more hopeful than that. The Bush administration in December said that India could export generics to India—I'm sorry—to South Africa, and we would not object under TRIPS. Under TRIPS you need to be a state to object. And there's actually a history at this point that the Clinton administration had a previous executive order about the interpretation of compulsory licenses. So, I mean there is a sense in which the developed countries have said in very explicitly, or at least the American government has, we're not going to push this joke to its natural limits. There is a little bit of evidence that public pressure can shape how TRIPS actually emerges.

MR. BARTON: Let me add a little bit to that. First of all, compulsory licensing almost never happens. And its main role is not to happen. Its main role is to be a bargaining chip to encourage a price concession. I think there's no question about that.

MR. SIKKA: Absolutely.

MR. BARTON: And the pharmaceutical industry is under the political pressure of the last several years, had moved towards very substantial donations and so forth of products for sub-Sahara Africa. I think it's clear these are nowhere near enough to satisfy the supply. I think there's a real question and this I think is one of the important issues for the future about the sustainability of that kind of donation or strongly discounted price arrangement on a voluntary basis. But the—so the compulsory licensing provides its fundamental role in encouraging the pharmaceutical industry to do that sort of thing.

In terms of debate over the details of TRIPS, the technical problem ends up, what do I do when everybody has their patent systems, which many of them are supposed to by 2005, and I don't have the Indian generic industry? In other words, at this point, the Indian generic industry can

supply products to sub-Sahara Africa even in countries where products—where a product is not patented. Now, the realities as I understand it are, this is actually only a small percent of the market because there are many other real problems, including the health care and maintenance problems and so forth that have already been described. This is one of several problems in a series. But, that and the availability of that industry to do that with products that are still on patent in the majority of the world will change in 2005. And so we're going to have a very different world at that point.

DR. VON MORZE: I comment on that point because the change only applies to patent applications that will be filed in 2005, and from what we heard about the research and development, it will take it to at least 2015 before—because you have to have a product that is being developed, that is put on the market, and then it would be subject to a compulsory license regime or some sort of regime. But it takes still quite a lot of time before the change will be effective.

MR. BARTON: You had a question.

AUDIENCE: Thank you. A lot of these countries in the developing world have large populations of people, so I presume that their incidence of the disease would be higher. So my question is, that whenever you're working on differential pricing and looking at return of investment, how much of those higher incidences are taken into consideration?

MR. MAURER: I think everyone looks at the ultimate market and depending on how much is purchased and at what cost. So yes, if you can—and you get the return. Indeed, if you're looking at vaccines, we certainly don't have to do much advertising in places like sub-Saharan Africa for an AIDS vaccine. It's a matter of getting your eighteen wheeler trucks loaded up and shipped off to the nearest airport or boat and shipped off there. So, I think, yes, the tiered pricing that we discussed a little bit for things like vaccines is straight forward. As a matter of fact, even in the United States, vaccines are tiered priced to the pediatrician's office versus the government, where you don't have any marketing issues. You just send it off to a government warehouse. So, in that case, the situation that you actually point out, you're selling a lot more product, yes, per unit cost is less, but your profits can be substantial. What I'd mentioned before was that especially when you don't—these kind of manufacturing plans are very expensive to do. And so when you—early on, it's got difficulty—even though your running it 24 hours a day, you get \$5 a dose profit here, 50 cents a dose there. What's your board of directors going to say?

MR. BARTON: There's also a whole phenomenon of UNICEF and a group of institutions working with it buying the vaccine products for

distribution in the developing world. When you hear about the field day campaigns of stopping the Civil War somewhere and trying to vaccinate everybody under X years old, those are typically run by the international donor community, and that community is usually able to get—no, the older vaccines, of course. It's able to get those older vaccines, you know, on the order of one percent of the price that my kids pay for their kids to have it. And, this reflects buying power. It reflects taking advantage of surplus capacity of vaccine manufacturers in Europe in order to try in essence to get the price basically at marginal costs plus minuscule, meaning that the capital costs of operating the production plants and building the production plants, that all has to be borne by the parents of the children in the U.S. and Europe.

AUDIENCE: Probably an undue able experiment, but I am just wondering if tomorrow, if all patents are held invalid and there is no patent regime in this country, what do you think would happen with all the biotech companies? Would they all close up shop and go away?

MR. WINTERS: You would be raising money, for sure.

MR. MAURER: The existing large biotech companies have large cash reserves and trade secrets upon which they can rely so they would become smaller but probably still be viable. The industry as a whole, the biotech industry, is just focusing on that narrowly, still loses money. So all the start up companies would just go away. Because if you talk to venture capitalists or executives from start up companies what you find is that what the venture capitalists are interested in is patent protection. And they will have due diligence teams that come and assess those patents and try to determine whether or not the protection those patents confer justify the investment. And the trade secret is sort of, there are people here with more experience in this than me, but as I understand it, trivial for V.C. [venture capital] investors. That would bring an end, in large part, to the biotech industry. And that was one of the, the subtext of the remarks I gave. I think there's a reasonable case that can be argued that without patent protection for gene sequences here in this country, because as we've heard repeated a number of times today, a lot of companies focus only on this market, there's a credible case to be made that the biotech revolution would simply not have happened.

MR. BARTON: Other questions?

UNKNOWN: I think we actually have to wrap up. If anybody has any additional questions, maybe they can ask the panel members directly. We really thank you all for coming.

MR. BARTON: Okay. Well, thank you.

