SYMPOSIUM ON BIOINFORMATICS AND INTELLECTUAL PROPERTY LAW

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THE PROPER SCOPE OF IP RIGHTS IN THE POST-GENOMICS ERA

PROFESSOR MILLER:

Our presenter this afternoon is Professor Arti Rai from the University of San Diego School of Law. Professor Rai attended Harvard Medical School before focusing on the law, in a reversal of pattern that seems very familiar, at least to me as a health law professor now. We do now seem to get an awful lot of physicians wanting to become lawyers. She served as executive editor of Harvard University's *Civil Rights-Civil Liberties Law Review*, and clerked on the U.S. district court for Judge Marilyn Hall Patel. She was an associate at the Washington, D.C. office of Jenner and Block, as well as an attorney with the U.S. Department of Justice. She has taught health law at the University of Chicago Law School and was a Faculty Fellow at Harvard University's Program in Ethics and the Professions.

Professor Rai joined the University of San Diego faculty in 1997 and teaches and writes in the area of intellectual property, biotechnology and the law, and health-care regulation. She is the author of *Rationing Through Choice: A New Approach to Cost-Effectiveness Analysis in Health Care* in the *Indiana Law Journal*, various other law and medical journal articles, including one in our *American Journal of Law and Medicine*, which is published here at the School of Law. She is a co-author of *Law and the Mental Health System*, a West Publishing Company publication, and serves on the Board of Editors of the *American Journal of Law and Medicine*.

PROFESSOR RAI:

My talk on bioinformatics is going to be quite a bit different, I think, than some of the others we have heard today. For the most part today we have been talking about intellectual property in the context of the cumulative research process that is biopharmaceutical innovation. I am going to talk not so much about bioinformatics and intellectual property in the research process but more

about how bioinformatics might affect intellectual property rights in end-product pharmaceuticals. Needless to say, because I am talking about pharmaceutical patents, I will probably be touching on some politically charged questions. To some extent at least, some of those questions are somewhat off-topic because they are questions that are really raised by the demand side of the pharmaceutical industry. They are questions about whether and how we should ensure that all people have access to pharmaceuticals, or at least some set of pharmaceuticals that are considered essential for health care purposes. Those are demand-side, insurance-type questions to which Fran Miller could probably also speak, but I would be happy to talk about those issues in the question and answer. Since this is an intellectual property and bioinformatics conference, however, I want to keep the focus in my talk on the supply side, that is, on how bioinformatics developments will affect or could affect research and development and, as such, could provide us some food for thought in terms of how we think about end-product pharmaceutical patents.

In many respects, my thesis is quite simple. Right now, we have a very specialized regime of intellectual property protection for pharmaceuticals. This has been justified on the grounds that innovation in this area is quite a bit different from innovation in all other areas. First of all, the basic research is uniquely risky and expensive and, in addition, the FDA-mandated process for drug approval is extremely risky and expensive. So we need the byzantine regime, that is, not only the specific provisions in the Patent Act[1] itself, but also the Hatch-Waxman Act.[2] We also need, as I will point out and have in the past, a significant amount of federal subsidy for the basic research that is involved in developing pharmaceuticals. My thesis regarding the promise of bioinformatics is that drug development will become less unique as time goes on. It may not become just another information science, but it could become less unique such that we may need a regime of protection that is less unique than the current regime. To put the point another way, there may be less reason in the future to accommodate claims, which I think are quite legitimate right now, that the pharmaceutical industries uniquely rely on patent protection and, thus, need all the special protection that is provided by statutes such as the Hatch-Waxman Act.

Before I go any further, I do want to throw in a caveat, and that is that in the area of biotechnology, in general, over the last twenty years, all predictions have had an irritating habit of being completely wrong. Unfortunately, this is particularly true of optimistic predictions. Only a few years ago, we heard that gene therapy would be the wave of the future, and gene therapy, as some of you may know, has yet to yield a single, marketable product. Even more recently, we still thought that the one-gene, one-protein hypothesis was, more

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[1] 35 U.S.C. § 101 *et seq*. (2000).

[2] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 15 U.S.C. §§ 68b-68c, 70b (2000); 21 U.S.C. §§ 301 note, 355, 360cc (2000); 28 U.S.C. § 2201 (2000); 35 U.S.C. § 156, 271, 282 (2000)).

or less, correct, and we thought we had 100,000 genes. Well, as it turns out, we have much less than that. We have about 30,000, and each gene codes for multiple proteins, as we learned this morning. So anyone who is going to talk about how genomics may shape research and development in the future should be very humble and should say, "Well, there are lots of caveats," and say, "I do not mean to suggest that this is necessarily going to happen."

Also, in the last few months, there have been a slew of reports from various consulting firms, including McKinsey and the newly-named Accenture firm, which used to be Andersen Consulting, talking about how we are hyping bioinformatics far too much. They predict it is going to take a long time before the bio-pharmaceutical industry learns enough to realize any of the purported efficiencies that should be created by bioinformatics. In large part, this is because the biological system is an information system that is uniquely complex and unpredictable and non-linear. Finally, last but not least, there is a possibility, which works as another caveat for purposes of my assertion, that we will have more efficiency in the future in pharmaceutical development. This is the possibility that a field of research known as pharmacogenomics, which I will talk about more in a moment, will divide the market for particular drugs and, thus, make them less profitable.

So with all those caveats as background so that no one can accuse me of being unduly optimistic or Pollyannish, let me lay out a sketch of how bioinformatics could possibly make pharmaceutical development more efficient in the not too distant future. Then, towards the end of my talk, I will discuss how if this prediction does come to pass, we may then want to think about changing the structure of our pharmaceutical patent regime, so as to make it a little less byzantine and less unique than it currently is.

As we all know, current drug development is a laborious, expensive, and risky process. Traditionally, before bioinformatics, we had very few targets to work with, and identifying targets was something that was done in the wet lab and often took many years, and that was just the pre-clinical stage. Then, there was the elaborate clinical testing stage that was necessary for purposes of determining safety and efficacy. Clinical testing is, of course, FDA-mandated and there are three stages of it, with progressively larger groups of individuals. One of the reasons that clinical testing, in particular, was so expensive, or has been so expensive, is that drugs often fail at the so-called "Phase III clinical trial stage." This is the stage that involves thousands of individuals and so obviously enough, if a drug fails at that stage, you have already expended a huge amount of money in developing that drug. The reason that these drugs typically fail at the Phase III stage is because they either have adverse effects, or sometimes no effect at all, on some sub-group of that particular disease population. That is how we get the figure that is often cited by the pharmaceutical industry to the effect that drug discovery development and testing can take about 10 to 15 years and cost $400 million or $500 million per successful product that makes it to market. That is the pre-genomics picture and, to some extent, is still the picture today.

What would be an idealized model of drug development in the

bioinformatics era? Well, it would be similar to some of the things that Andrew Marks talked about this morning. At the pre-clinical stage, we would do most of our investigation, or a lot of our investigation, at least, on a computer rather than in a lab. For example, at the pre-clinical stage, one approach for identifying targets would be to look at differential gene expression in the cells of people with particular diseases and then determine, based upon that differential gene expression, or identify, based on that differential gene expression, genes that might be implicated in that particular disease. The technology that would be used would be DNA chip or micro-array technology. That would be for the purposes of target identification. At that point, once we had identified a possible target, we could also look at its function by inputting the gene sequence into databases which would help us determine if there were similarities or homologies between that particular gene sequence and previously-sequenced DNA and thus give a sense of function.

At the clinical testing stage, we may also be able to realize some efficiencies through the use of bioinformatics. This is where a lot of the attention has been focused, at least in the more popular literature on bioinformatics. As I mentioned, drugs often fail clinical testing because they either have adverse effects or no effect on some sub-group of the population that has a particular set of clinical symptoms of phenotype, i.e., disease. Perhaps not surprisingly, in many of the cases of adverse effects, the individuals in question have small genetic variations, known as single nucleotide polymorphisms, or SNPs, in genes that are important for drug metabolism. What happens is that a particular SNP, for example, may cause you to be a fast-metabolizer or slow-metabolizer and, as a consequence, the ordinary dose of the drug is not appropriate for you. It either kills you, or it could have very serious side effects.

In the past, we had no idea who would have these adverse effects and who would not. Thus, the test population included everyone with a particular illness. The promise of genomics is that knowledge of SNPs will help us identify those individuals who are likely to have adverse effects because we will be able to identify whether they have SNPs affecting important drug metabolism gene loci.

What about those individuals with a particular disease on whom the drug has no effect? Well, SNPs are also at issue here but, here the SNPs are typically not within drug metabolism genes. Rather, we have a variety of SNPs that are either responsible for or associated with differential genotypes within that clinical phenotype that presents with a particular disease. Thus, even though the disease may look to be singular, on clinical examination it actually represents a number of different phenotypes. SNPs screening technology is also going to be useful in this situation because it can identify those individuals and particular genotypic sub-types of phenotypic categories to which they belong. The populations in clinical trials can then be subdivided so that the clinical trial will only test a given drug on those individuals who have a SNP profile conducive to response to the drug, either because they have the appropriate drug metabolism genes or the appropriate sub-type of a given

phenotype. The result of all this, in an optimistic version of this tale, is that we will be able to prove efficacy through faster, smaller, and cheaper clinical trials.

I mentioned earlier that the SNP-based technology I have just been describing is often categorized under the heading of pharmacogenomics. I also mentioned earlier that pharmacogenomics, although it has been touted as a mechanism for reducing the cost of drug development, also has the potential for dividing the market for particular drugs. Here, the argument would be that any reduction in the expense of clinical testing will be wiped out by the smaller population for any given drug. I have given some versions of this talk before in audiences that have a lot of pharmaceutical industry types in them, and the objection you always encounter is, "Well, fine. So pharmacogenomics may help us in terms of the cost of clinical trials, but you will have such a fragmented population that your market base will be reduced, and that will wipe out any efficiency gains on the clinical-trial side." I think this objection is a little too facile, although, as I will note, it has some validity. In cases where SNPs affect drug metabolism genes, SNP variants do not necessarily have to prevent a person from using the drug that is marketed for a particular phenotype. They just change the appropriate dosage, in that context. Thus, not all SNP-based drug development is going to end up dividing the market in the way that I think the pharmaceutical industry fears.

Now, it is true that when SNP variations affect an underlying genotype and show that a particular disease is, actually, not one disease but five different diseases, for example, there is the possibility of dividing the market. Even here, however, at least in certain situations, we may be dealing with a context in which there is a majority and a minority group. At least for the majority group that has a particular sub-complement, the number of people in that group may be relatively large. Of course, we might have a small group that unfortunately demonstrates another genotypic profile and will not respond to the drug that is marketed for the larger group. As I have talked about in some other work I have been doing, they will probably, then, become an orphan group and could be treated under the Orphan Drug Act.[3] I do not think that the benefits of pharmacogenomics in terms of increased efficiency in clinical trials are necessarily going to be outweighed by the risks of dividing the market. Also, needless to say, from the perspective of the consumer, they are probably better off not being part of a market base for a drug that would have been either useless for them anyway or would have had adverse effects on them. But that is sort of a side point.

Moving to legal analysis, how should the law, specifically the regime of intellectual property rights for pharmaceutical development, respond if, in fact, we do see that efficiencies are being realized in the pharmaceutical development process? Well, one thing the law can and should do, even prior to any evidence of efficiencies being realized, is not stand in the way of the

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[3] 21 U.S.C. § 360aa-360dd (2000).

possibility of these efficiencies being realized. We should do our best to try to alleviate patent thicket or so-called "anti-commons" problems that might arise because multiple pieces of genomic information that are going to be crucial to drug development are patented by different parties.

As previous speakers have discussed, where we have multilateral monopolies, the situation is ripe for really high transaction costs and probably bargaining breakdown. I do not want to spend a lot of time talking about ways to avoid the thicket or anti-commons problem because that is something on which other people have touched. It seems to me, however, that we are beginning to see some promising mechanisms for addressing anti-commons problems in the form of public and private entities' disclosure of relevant genomic information, which can prevent other parties from seeking patents on that information. It may also be possible, although the arguments that have been suggested may not work as well, to set up patent pools in the context of the biopharmaceutical industry. Finally, it seems to me the trend that we are seeing in the biopharmaceutical industry towards increasing vertical integration, either through mergers or through tightly linked strategic alliances, might have the effect of reducing transaction costs, thus alleviating the anti-commons problem.

As I said, though, that is not really what I want to focus on. What I do want to address is how the law might react if some of the efficiencies I have suggested arise in the drug development process do become reality.

The most important feature of pharmaceutical protection that makes it different from protection in other areas is, as I have suggested, the Hatch-Waxman Act. Now, most people who have heard of Hatch-Waxman know that it extends the patent term for drugs. The idea is that because the drug's patent term is typically running while the drug is in the FDA approval process, manufacturers need to be compensated for the unprofitable, and, in fact, costly, time they spend in that process. This is hardly the most anti-competitive feature of Hatch-Waxman, however. In fact, this feature of Hatch-Waxman, it seems to me, actually could be viewed as bringing pharmaceutical protection in line with protection for other invention, given that most other invention does not have to go through this regulatory process before it is marketed. The features of Hatch-Waxman that are of concern to me are those features that provide incentives for drug manufacturers to seek not just one patent on a drug but multiple patents, particularly several years before the basic patent that has received the Hatch-Waxman extension is set to expire. These additional patents that drug companies seek are often quite frivolous in that they claim unimproved indications for a drug or specific drug formulations or even, in some circumstances, tablet shape. No matter how frivolous a patent is, however, it can provide a defense against competition.

Normally, it would be difficult for a truly frivolous patent to provide a defense against competition because if the party wanted to enforce the patent, for example with a preliminary injunction, it would at least have to make a colorable claim showing that the patent could be valid. Under Hatch-Waxman, however, the drug manufacturer does not have to do that. This is because

Hatch-Waxman sets up a regime in which the patent statute is linked to the FDA regulatory approval process, and as soon as a brand-name manufacturer brings a claim of patent infringement against a generic competitor, the approval process for that generic competitor is automatically stopped. In fact, there is an automatic thirty-month delay in the FDA approval process for the generic competitor at that point. Essentially, what the brand-name manufacturers get is the equivalent of an automatic thirty-month preliminary injunction, without having to prove anything, and that is not even the worst of it. During this thirty-month period, brand-name manufacturers often succeed in further delaying generic competition by entering into settlements with the generic manufacturer not to market the drug until all the applicable patents, frivolous or not, have expired.

Because of Hatch-Waxman, the brand-name manufacturer does not have to settle with all potential generic competitors. It only has to settle with the first generic competitor because that first generic competitor is given a 180-day exclusive marketing period, and this marketing period is not even triggered until generic marketing actually begins. The bottom line is that settling with a single, generic competitor forestalls all competition from any competitor until 180 days after the relevant patents, frivolous or not, have expired or are declared invalid by a court. Since you have settled with the first generic competitor who challenged your patent, somebody else has to come along and challenge your patent and get it declared invalid. Then, only after 180 days of exclusivity for the first generic can others begin to market their generic drugs. Thus, we are talking about a very significant chit that is given to the pharmaceutical industry through this particular structure in Hatch-Waxman.

Now beyond Hatch-Waxman, drug manufacturers also enjoy a significant subsidy because the basic research it uses is often funded by the federal government. Because of the technology transfer legislation passed in the early 1980s, drug manufacturers can often seek, or at least acquire, exclusive rights in this research. The rationale for these tech-transfer statutes, as Rebecca Eisenberg has discussed at great length in her work, basically follows Edmund Kitch's view of patents as prospects for development. On the Kitchean model, patent rights give industry an incentive to engage in the investment necessary to develop the research into a commercial invention. In the particular case of pharmaceuticals, the critical development time, for which property rights are needed, is the period necessary to translate the basic research into an invention that is ready for clinical testing. At that point, at the clinical-testing point, the drug itself becomes the subject of an independent patent.

To the extent that bioinformatics does produce efficiencies in the drug development process, we could think about altering the protectionist regime for pharmaceuticals that I have described. When I say protectionist, I do not mean the term in a pejorative way. I am merely acknowledging or describing a reality that is out there, that pharmaceuticals are protected much more heavily than are other inventions. So for example, we could think about – and some legislation currently in Congress is already beginning down this road – eliminating the automatic thirty-month delay in the generic approval process

that gives brand name manufacturers an incentive to file additional frivolous patent applications to extend protection of their drugs. We might also require generic manufacturers to forfeit marketing exclusivity if they settle with brand name manufacturers and decide not to market.

If very significant reductions in research and development costs are realized, particularly at the preclinical stage, we might then think about the federal subsidy for pre-clinical development provided by Bayh-Dole[4] and other technology transfer statutes. In that context, perhaps it might be advisable to consider the idea that some percentage of the profit from drugs that are based on federally funded research should go to a fund that provides insurance subsidies for patients that do not have insurance for drugs. Another piece of the paper on which this talk is based talks about how insurance is really the key to access in this area. Insurance is really the reason why most individuals have more than sufficient access and other individuals do not, as contrasted with the reflexive view that some take that it is a problem of intellectual property rights. It is actually more a problem of insurance at the end of the day. The larger point of my paper, however, is that the discussion of intellectual property protection even for pharmaceutical end products may increasingly become a subset of the more general discussion of protection for information. Thus, to the extent that the regime of patent protection for information raises concerns, these same concerns will also apply to pharmaceutical end products. On the other hand, if pharmaceutical development is no longer uniquely in need of protection, then there is greater justification for doing away with some of the most *sui generis* features of such statutes as Hatch-Waxman.

Thank you. I welcome any questions. (*applause*)

PROFESSOR MILLER:

Thank you Professor Rai. This afternoon we have two more extremely well qualified commentators here. We have Professor Iain Cockburn of Boston University's School of Management and Scott Brown, who is Associate General Counsel for Millennium Pharmaceuticals, both of whom I would imagine have slightly different perspectives on all of this.

PROFESSOR IAIN COCKBURN:

I think Professor Rai has given us a very provocative presentation, so let me give some counterpoints to some of the issues she brought up and some of her suggestions. Taking a step back from particular issues about review of Hatch-Waxman and the specific policy proposals which are bundled into Professor Rai's quite complicated paper, let us look at the economics of drug discovery in a broader perspective. The starting point for doing this, I think, is to look at the old model, which genomic medicine is supposed to supplement or supplant.

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[4] Bayh-Dole Act of 1980, 35 U.S.C. §§ 200-212 (2000).

This old model of discovery and development of small molecule drugs, mostly through the application of the chemistry and biology of the 1960s or 1970s, is one that actually worked pretty well. The payoff was a "golden age" for the pharmaceutical industry, which produced hugely successful drugs such as Prozac and Zocor. As we prognosticate about the impact of genomics and a new economic organization of drug discovery, I think it is worth posing the question, what was broken about the old regime? What might be staying broken, and should we be trying to fix things?

By most economic indicators, the old system worked extremely well in the sense of generating a lot of improvements in human health and, as we are pleased to note down at the business school, excellent returns to investors in the companies who mastered this technology. By any measure, this "golden age" was highly productive, and this success was, I think, driven by a variety of factors and institutions. The nature of the downstream market, and of regulatory scrutiny, played an important role in providing research incentives and shaping competition, and at the same time the industry was supported by substantial contributions from not-for-profit academic and government research, enabled by the Bayh-Dole Act and sustained public sector investments in basic research. But now we are living in a new world in which the division of labor in research is not so clear anymore, in which the downstream marketplace has changed a lot, with the rise of managed care, etc., and in which the pharmaceutical marketplace has a much hazier future. With these considerations in mind, let us look at the questions raised by the appearance of pharmacogenomics and genomic medicine in general.

I think there certainly is a real possibility that, as Professor Rai suggests, the time it takes to develop new drugs might indeed be decreased by these new technologies. It might also be the case that the cost of new drugs will fall in the sense that drugs will get a lot better, the quality will rise, and then in a quality adjusted sense, the cost of producing them will fall. I am much less optimistic, however, that the amount of dollars involved is going to shrink, and, in fact, we just need to look out of the window here to see many billions of dollars going into tooling up for this process. I agree that we may see an acceleration of development times through introduction of these new drug development technologies, but at a very substantial cost. One feature of the Old World was that there were roughly 400 or 500 physiological targets that everybody was chasing after; in the New World, people are talking about 5,000 or 10,000 buttons to potentially press around the human metabolism to try to get desired results. As a result, I think we are going to see many, many more drugs being brought forward, all of which are quite expensive to produce. Even though trials might be shorter, more accurate, and easier to conduct, I think that we are going to see the research and development budget of projects directed toward the end user just going up and up and up.

That is one side of this problem. Another side, I think, is to think about what downstream competition will look like in these markets. If we are going to get a "fractalized" drug market with medicines being increasingly targeted and more specific, directed at smaller and smaller populations, I think this is

indeed going to affect the economics quite dramatically. If you look at the significant expenditures for today's successful pharmaceutical companies, some of it is research and development cost and a big chunk of it is marketing and distribution activities. All of these, from an economic perspective, feature substantial economies of scale. I think that trying to serve smaller and smaller markets that get harder and harder to identify is actually going to raise costs per drug substantially. Orphan drugs may be the right model for this new wave of products, and orphan drugs are the ones which seem to have needed special incentives from the regulation or intellectual property side in order to make them economically feasible.

Another interesting aspect of this is that there is a collapsing of the distance in time and in economic space between bioinformatic or genomic research and the marketplace. Shorter development times and an increased role for "retail" genomic information, (as opposed to the "wholesale" upstream market in the research and development sphere), are going to change incentives and competitive behavior quite dramatically. If we are each going to need special drugs to suit our genetic profile, testing technologies are going to become a significant retail product, and new distribution and delivery technologies are going to be necessary, and none of those are going to be cheap. I think there is going to be a tough-fought battle for the rents associated with this new technology, involving significant investments in manufacturing, distribution, and marketing along with R&D, and I do not necessarily see this resulting in lower costs or prices.

Those are some of my thoughts on the connection between this new technology and costs and pricing. I think that moving on from that to what should we do about forthcoming debates on Capitol Hill about Hatch-Waxman is a big leap. It is going to take a decade or so for the economic impacts of all this new technology to spin out . The success of the industry in gaining Hatch-Waxman provisions, I think, is a separate debate somewhat orthogonal from this question of what to do about genomics.

While I have the microphone, let me just put my five cents into some of the issues that have come up over the course of the day, and say something about the role of IP in biomedical science. In the "golden age" we had a relatively clear division of labor in research. Basic science and information was generated in a not-for-profit world which ran under its own unique set of incentives and funding mechanisms, namely the universities and the NIH. Formal IP rights played a very limited role in this world of "open science." By contrast, applied research was done by a commercial sector in which IP rights played a very important role in generating incentives and protecting investment. What we have today is a new organization of the industry in which an intermediate sector has appeared, where people are doing basic science or producing research tools and information products (which have primarily a research use) on a for-profit basis. I have not heard much today on how intellectual property law and practice might be changing to accommodate this new model, or how these changes might play out in terms of the future productivity of whole system, and I think we need to be very careful here.

Casting back to the good old days before every assistant professor in the biomedical sciences had a startup biotechnology company presents a stark contrast to the new world we are beginning to see, a world in which IP rights in every new piece of information or every new discovery are viewed as being a potential source of great personal enrichment. By extending the domain of patents we may be undermining "open science" in ways which result in the killing (or at least crippling) of the goose that laid the golden eggs.

Putting these concerns aside, it is worth looking at how IP rights have been affecting the way in which this science-for-profit research tool sector has been operating. One of the things it has operated on is what you might call funny money, based on issuance of IP rights. Because this activity is taking place at a great distance from the market place, where insurers and patients are spending real money, conventional financial metrics for guiding investment decisions are largely useless. In fact, any attempt to calculate the economic return to date of all the venture capital that has gone into biotechnology is going to make Series I savings bonds look compellingly attractive. (*laughter*) Now, the best is probably yet to come, as the industry has been saying since 1978. I believe that may be true, indeed, the best might be just about to come, and it might be a really good time right now to invest in companies like the ones we can see out the window here. Nonetheless, we should recognize that extracting real economic returns from science is a tough problem, and one which patents may not be the best answer to.

Extending the domain of patents into the arena of basic science has had a number of effects. One has been a surge of investment as companies have raced to obtain proprietary rights over genomic information and associated research tools. Another has been the rise of patents as a currency in trade in brokering deals, and in valuing companies with no immediate prospect of revenues. In this world of reach-throughs, cross-licenses, and sprawling patent portfolios it is, I think, very hard to evaluate the actual value of IP rights, or the long run impacts of changes in IP rules on incentives to invest. And ultimately, of course, we care about the impact of IP on economic outcomes, on efficient resource allocation. As the biotechnology industry matures, and real dollars revenues start to appear on the table I think we are likely to see a wave of consolidation and restructuring, accompanied by a re-evaluation of IP rights and an intensification of struggles over the economic value associated with genomic medicine. Concerns are likely to arise regarding who is holding monopolies over research tools, and where, and what the implications of contracting difficulties, stacked royalties, and double or triple marginalization are for the costs of drug development. I think that "vertical" struggles over the payoffs from genomic information and associated science are unlikely to reduce costs or lower risks, in which case I think we need to be even more cautious about the impact of tinkering with the regulatory environment. In the end, higher margins and longer periods of market exclusivity may be needed to make sure that all of the players in the chain of drug development have adequate incentives to do R&D, in which case the policy changes which Professor Rai has been talking about might be precisely the wrong response to the rising importance of genomics.

Thank you. (*applause*)

SCOTT BROWN, ESQ.:

I want to start my comments in stressing what by now should be pretty obvious: how important patents are to the pharmaceutical industry. Everything that has been said about the reasons and the economics, the expense of clinical development, the expense of discovering and finding new drugs, holds true, but the industry in large part is driven, as much as some would like to deny it, by our ability to recoup those expenses and make a profit at the end of the day. The figures that have been thrown out are pretty accurate: $500 million plus to get one drug on the market. That includes the cost of failures along the way, but in essence, $500 million, $600 million are figures that are not so far off. Another figure I would like to throw out that is instructive of how the process really works and dovetails into how pharmacogenomics, genomics, bioinformatics is going to change the drug development process is that right now, pharmaceutical companies will literally look at dozens of dozens of compounds, at least in the old regime, as pharmaceutical targets for a given disorder. Twenty-five of those dozens of dozens will ever get to the point of actually testing small molecule compounds against the target to see if they might work as a possible drug. Out of that twenty-five, if you are lucky, ten

will ever see the beginning of clinical trials, and with more luck, one out of that ten will see the light of day in the marketplace.

Where pharmacogenomics, where genomics as whole, proteomics, and bioinformatics are going to affect that process is by putting more into the beginning of that queue. Now, Millennium and companies like us are not looking at dozens of dozens of targets, we are looking at thousands and thousands of targets to fill in that queue. But unfortunately, since nature is a bit of a cruel mistress, what is not going to change is that dynamic of moving from the twenty-five that look like they are going to be really good targets to the ten that get to the clinic to the one that sees the light of day. Pharmacogenomics in large part is going to increase what goes into the beginning of the hopper, and it is going to be a useful tool to help us pick which compounds are better to put into the actual drug search process. There is not going to be – ever, I believe, and the scientists that work for us, I think, are of the same mind – a substitute for testing in animals and testing in humans. We are never going to get away from that, and so the long process of going through clinical trials, dealing with the FDA, is not ever going to disappear. In fact, probably the vast majority of it is going to stay the way it is.

Things like pharmacogenomics are going to help us pick patient pools. We are undertaking large pharmacogenomic efforts at Millennium, and our plan is to do just that. To put it in a crass way, we try to clip clinical trials. Let us pick the patients we want to put in so we can get a smaller data set, which means fewer patients, less time, less money. We want fewer patients going into a trial to try to prove efficacy. Find those people that have safety risk factors and eliminate them from the trial. That is something that again is going to help costs go down, but when push comes to shove, we are a long way off from pharmacogenomics evolving to the point where we are going to be able to be that selective in that many clinical trials. There is going to be a long lead time where we are still going to have to do it the old fashioned way, the way we have done it since the golden age: throwing the compound at test subjects, seeing who reacts and who does not, and trying to get a side effect profile. That is acceptable, and unfortunately most of the time it does not happen. Either the side effects are too bad or the efficacy is not such, and nothing we can do to predict that will change that.

Thus, even though we are increasing, through these efforts, what is going in the front of the hopper, protecting those tools we use to parse through all this information and find targets worth the tremendous expenditure is critical in getting a return on our investment. One thing that troubles people a lot, however, is the sheer volume of what we are discussing. In the golden age, pharmaceutical companies had a few handfuls of patents on targets; biotechnology companies had a few handfuls of targets. Unfortunately, now there are a few handfuls of companies, and we are among them, that have thousands of patents that cover, as some people would say of people like our competitors at Human Genome Sciences, the entire human genome. They think they have covered everything that is relevant. We do not believe this, of course, but then we have a large part of what is relevant too. The fact that a

very few small players are making claims that they have that level of coverage over such a large spectrum of possible targets troubles people.

In fact, I think one of the things we are most worried about is not so much the technical aspects of what we should be doing economically or what the patent system is going to do. I am more concerned about public opinion, to be perfectly honest. The hue and cry that is out there that genes should not be patentable, and that all these research tools as a whole should not be patentable. That is the debate that worries me more than anything else. In fact, our friends the Judiciary Committee are taking this up again in about ten days. On May 8, there is going to be another hearing with Orrin Hatch and the judiciary crew trying to decide in debate whether we should do something about making all this patentable at all. That is what keeps me awake at night, worrying about whether that train is going to keep steaming down the track and remove all incentive here from at least one perspective.

If the patent protection for these types of tools, bioinformatics tools, pharmacogenomic efforts, genomic efforts comes to a halt, then the entire balance that my two panel members have talked about will come undone. It is not that drugs are not going to get made – drugs will be made – but the entire economic balance changes if all targets are open to all parties. If all targets are freely available to everyone, it changes this dynamic. You can just imagine the choices that are going to be made differently. To spend $500 million to develop a drug – because that cost figure is not going to change very quickly – when anyone can come along, choose the same targets, pursue the same targets, pursue the same drugs becomes an extraordinarily risky endeavor. I think we have to be wary of tinkering with the patent system and changing that economic balance. Maintaining at least some monopoly with respect to the drugs that we make and the targets we are pursuing works. Drugs are getting made. Pharmacogenomics is going to allow more drugs to be made. Genomics is going to make more drugs get made. We have to be careful about tearing down the patent system to either shorten exclusivity periods or limit protection as a whole, or else the wheels are really going to come off, and the choices to make drugs are going to get harder and harder to make.

There are a couple comments that other panel members made that I wanted to touch on. There is a lot of talk about whether we should reform what Hatch-Waxman has done. Again, I think tinkering with that is dangerous, but I would also like to remind everyone that all those reforms, with regard to patent term and what generics can and cannot do, a lot of that was started at the impetus of the generics industry. That was not something that the pharmaceutical companies started. That was something the generics started because early on, they were concerned that they were not able to get started with their clinical trials and do the work they needed to do, as patents were construed to exclude them from doing that until after their expiration. Section 271(e)[5] provides an exemption from infringement, allowing generic companies to use patented

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[5] *See* 35 U.SC. § 271(e)(1) (2000).

drugs for purposes of submission of data for FDA approval. With this exemption, generics may obtain approval to begin marketing their drugs upon expiration of the pioneer drug patent. Thus, I think where we are with Hatch-Waxman, whatever the need for minor tweaking, is the result of lobbying efforts on both sides.

The generic industry and the pharmaceutical industry have lobbied to a compromise that works pretty well for both sides, and if we start tweaking, we have to be ensured that the benefits that have come to the marketplace from allowing generics to get on the market sooner are preserved. There is always a quid pro quo in the legislative process. If we are going to take things away from the pharmaceutical industry, compromises are going to be sought from the generics, and I am not sure what affect it will have in the marketplace. The current dynamic has worked pretty well in getting us to where we are, and we just need to be cautious, not push too far to one side and create an imbalance.

One thing I also wanted to comment on a little bit further in the context of the public debate is the concern raised about the degree that genomics patents and bioinformatics research tools patents are going to be roadblocks to research progress. I think Chicken Little runs around a little bit and claims the sky is going to fall, research is going to stop, and nothing is going to happen because these patents are out there in the hands of everyone. I do not see that happening. I know as a pharmaceutical company we are on both sides of this fence. Obviously, we have research tools and target patents that we seek to enforce against others, but we are also operating within this realm ourselves. We are finding drugs and using research tools. We are able to go out with tools we are using and often negotiate deals that are acceptable with people that hold those patents. I think there are always drugs that will not get made because agreements cannot be reached, but I think as an industry, as a whole, we are doing a pretty good job at being reasonable, reaching accommodations, and paying proper compensation to one another in order to ensure that the path is clear of roadblocks. I think a little of the Chicken Little mentality that the sky is going to fall if patents are freely granted in bioinformatics, with research tools or genomic efforts, is a bit overblown.

Another comment that Professor Rai raised was that the drug process will become less unique so there will be less reason to accommodate claims for better protection and extended protection, which I think was really the thrust with regard to her Hatch-Waxman comments. I find that a bit troublesome. While the bioinformatics revolution and the genomics revolution is going to pour more things into the hopper, we still always run up against that backstop of having to test in animals and humans and undertake extensive clinical efforts. These are the prime motivator behind us wanting to maintain, as an industry, those patent terms. It is that five to eight year delay while we are milling about in the clinic and milling about the FDA that cause us to want to get that extended patent term and to maintain at least a reasonable period in which we can recoup our investment. I do not think the revolution in bioinformatics and genomics is going to change much because again that extended time period required for FDA approval still looms. It is going to

shorten the front end of that process, but once we get to the clinic I think we are still going to face those challenges that are going to drive us as an industry to want to maintain those advantages.

With that I think I will stop and let us go to questions. Thank you. (*applause*)

PROFESSOR RAI:

I just have a couple of quick responses. I do not actually disagree with a lot that was said by my commentators, ironically enough, given that I think they perceived themselves as disagreeing with me. I do not think we should make any changes until, if and when, we see some real effects of bioinformatics in the industry in terms of actually reducing cost or increasing efficiency and reducing the length of clinical trials and so forth. I would be cautious about changing the system prior to some demonstrated change in the research and development process. The reason I do not think the Hatch-Waxman debates are necessarily orthogonal to genomics is that any change in the regime of pharmaceutical protection, it seems to me, has to be justified by some change in the economic structure of research and development. I do not see the "gaming" of Hatch-Waxman as really any different from any other type of pharmaceutical patent protection. Since I do not attach necessarily a pejorative or uniquely pejorative weight to what is being done with Hatch-Waxman, it seems to me that in order to reform Hatch-Waxman we need to see something change on the production end of things. We should wait. Frankly, I think that we should wait to see something change in the production end of things before we even make attempts to reform Hatch-Waxman.

PROFESSOR MILLER:

I happened to sit on the Genetic Testing Advisory Committee for Harvard Medical School, and I have a sense now that I had not seen before the breadth of what was out there. Professor Cockburn's comments on the market for testing technology certainly rang a bell with me on the costs issue. I had no idea of the breadth of what was going on right here, and that is just in the Harvard research community. The health economist in me was just bowled over. What this is going to do ultimately in terms of costs is mind boggling.

SCOTT BROWN:

I have a response to your comment. We are a company that works not only on finding the drugs but also on trying to figure out what markers would tell us who is going to react best to those drugs. Our ultimate drug product paradigm is, having not only the drug, but also the test that tells who is going to react well to it. While you could say, great, you have to pay for a test again, we think the economic efficiencies for health care, the demand side, the user side, are helped out in that before right now, clinicians may have three or four

different regimens to pick for treatment. Right now they cannot tell which patient, other than on their gut feeling and well-intentioned medical intuition, which person is really going to react well to that drug. Thus, particularly with cancer, you try three or four different treatment regimens, each of which is expensive in and of itself, until they find the one for this particular patient that happens to work. We believe that the actual cost of testing will be less than the costs of two or three failed drug regimens, perhaps, per patient, that result until you find the right treatment, and with the health care industry such testing would benefit everyone. With a the test, you can say "For you, ma'am, this is the breast cancer treatment you should take," rather than blindly administering Taxol to no avail, only to try another agent if that does not work, and have two or three false starts, each of which is fairly expensive. That is where we think it will balance out in the end. It will actually be more cost effective even though you have a test plus a drug both for the patient and the industry in the end. That is our selling point.

QUESTION & ANSWER SESSION

PROFESSOR MILLER:

That would be my hope too. (*laughter*) I am worried about the transition phase. But anyway, questions. Yes.

Q: *AUDIENCE (PROFESSOR KARJALA)*:

I think what I consider to be the most perplexing product of intellectual property has been raised. Everyone talks about these incentives and bundles of rights and how the public, in turn, benefits from these new products, and then the patent expires after a certain limited time, but nobody, to my knowledge, knows how to calculate these trade-offs. The drug industry strikes me as a very good example to think about conceptually. I read a few months ago, probably in the *Wall Street Journal*, that if we got rid of the efficacy testing at the FDA and just tested for safety, and just let the market determine efficacy, we could reduce the costs from $500 million down to $100 million or $50 million or something like that. Let us just assume that is correct. I do not know if it is true or not, but if it is, we are making a dramatic reduction in the costs of bringing a drug to market. With continuing to grant exclusive rights for a patent, however, we do not change anything in the economics of consumption. I presume that a drug company would still be charging what the market would bear, even though you have this dramatic reduction in costs. I am just wondering, how do we go about thinking about the problem of modifying the patent law when we have a major change in the underlying economic structure? I know you are trying to think about that, but I do not know how to think about the basic question.

A: *PROFESSOR RAI*:

Well, as you know probably as well as I, there is no good economic answer to what is the question of optimum scope or term or any other feature of patent protection, so it seems to me we should not make any changes until we see changes in the underlying economic structure, and that is about all we can do. All we can do is examine the deltas, we cannot really, at least not as far as I have been able to discern thus far or determine, calculate in absolute terms at any point whether we are at the appropriate point on the curve. All we can do is figure out if some feature makes us think that we are shifting somewhere on the supply side of the curve and therefore we should shift the amount of protection as well.

Q: *AUDIENCE (PROFESSOR EISENBERG):*

Presumably, how profitable drug development looks determines how far you go in investigating and how many of these leads you chase down, how promising is it to you. Since these cost measures are always aggregate cost measures, you are always looking across the whole range of candidates, and you are never looking product by product, you are never going to get any sort of clean data. You will always pursue it to the point where it looks like a good investment, so I want to push the argument a bit further on this. The disconnect, it seems to me, between your normative proscription here and the shift that you are describing. I sort of agree with Iain. I think the Hatch-Waxman stuff you are talking about really has very little to do with the potential for changing the economics of drug development as a result of bioinformatics or pharmacogenomics or whatever. Listening to you describe the features of Hatch-Waxman, I do not know if I really quite believe your claim that you do not want to mess around with it. You are talking about being able to get effectively a thirty-month preliminary injunction based on a bogus patent without any likelihood of prevailing on the merits. I do not know if you are listening to yourself. You would think that there was something else that was driving you there. The fact that people are engaging the Hatch-Waxman Act is no different from any other aspect of drug development, but I think you changed your tune there, and I wonder if you really mean that. I wonder if you really do not want to look into some of these ways of engaging Hatch-Waxman that I do not think they were intended. All legislation has unintended consequences, but maybe there are certain things we do worry about. Maybe we do worry about frivolous patents being out there and not challenged for a long period of time while consumers are paying lots of money for drugs that should be off patent. I wonder if you – I thought you thought that.

A: *PROFESSOR RAI*:

It is just another way of extending your monopoly. The patent term is a monopoly of sorts in the drug area because you do not tend to get good

substitutes. Especially with respect to the thirty-month automatic stay, it was put in to respond to the fear that generics would file frivolous challenges to these brand name drug patents, and this thirty-month automatic stay was sort of a way of insuring that frivolous challenges on the part of the generic manufacturers were not filed, and so as a consequence now we have some frivolous patents on the part of the brand name manufacturer. It is just a way of balancing the interests of the generics versus the brand name people. I see that as just part of our system of intellectual property. I do not see that as being distinct in any –

Q: *AUDIENCE (PROFESSOR EISENBERG)*:

Maybe there is another set of stakeholders here who were not there negotiating the terms of Hatch-Waxman who would now like to be included. Maybe the cost of drugs is more on the radar screen of insurers, for example, than it was. Maybe now HCFA is going to want a way in. Maybe there are other people who are concerned. This may have been perfectly okay between big pharma and the generics, but somebody is paying the price for the deal they struck, and maybe they do not want to go on paying that price. I am not sure that any of this has anything to do with bioinformatics and pharmacogenomics at all, but I did not think you did either.

A: *PROFESSOR RAI*:

I take issue with the idea that Hatch-Waxman can be addressed sort of by itself, in a corner, without thinking about the larger structure of innovation, because as I said, I do not see a distinction between what is being done with Hatch-Waxman and what is being done in seeking patents to the largest extent you can, which is what all companies do under the prevailing patent laws. Even though perhaps my language seemed to attach a special normative weight to Hatch-Waxman, I do not actually intend to do that at all.

A: *SCOTT BROWN*:

If I take up my pharmaceutical company and file a patent, I think some of the balances that ended up getting struck in Hatch-Waxman are a little curious in and of themselves. I also I think certainly some of the monkey business that is going on was clearly not intended. The one I point to where you buy off the first guy, put a moratorium in place, and –

A: *PROFESSOR RAI*:

I actually think that piece of it could be addressed and is being addressed by the FTC.

A: *SCOTT BROWN*:

You see them coming down on that.

A: *PROFESSOR RAI*:

Right, that piece of it I actually think is being addressed and will be addressed.

Q: *AUDIENCE (PROFESSOR EISENBERG):*

It is self-enforcing. To the extent that bioinformatics shortens drug development times, that is taken care of automatically by the original provisions of Hatch-Waxman. It gives one extension if you do not have –

A: *PROFESSOR RAI*:

Right. That piece of Hatch-Waxman, I think, is actually necessary in order to make pharmaceutical protection comparable to protection in other areas, so that piece of it is not something that I think is problematic or will be problematic, ever, because it is also self-correcting.

Q: *AUDIENCE (PROFESSOR EISENBERG)*:

Right, although I do not really know if what is going on in other areas is necessarily the right benchmark –

A: *PROFESSOR RAI*:

Oh, right, I know, that was a piece of what I wanted to say at the end, that our system of protection for information generally may be terrible, and maybe to align pharmaceuticals with that may be terrible also, but there is no reason to have differential treatment if the path of innovation is similar in all these different areas.

A: *SCOTT BROWN*:

Again, taking off my pharmaceutical hat and putting on my metaphysical patent law hat, the seventeen-year and now twenty-year patent term, that evolved a long time ago. It was back when technology moved a lot slower than it does now, and where in order to get economic return on your investment took a lot of time, and technology meant something for a longer period of time. Today technology is changing so fast that I think if we want to look at policy in this area – again, here I am working for a pharmaceutical

company saying this – we need to consider whether twenty years in today's world of technology is too long.

A: *PROFESSOR RAI*:

Although would you say that for the end product pharmaceutical as well?

A: *SCOTT BROWN*:

Again, just in a metaphysical patent law sense, (*laughter*) I think the way that we handle pharmaceuticals, which Hatch-Waxman tries to do, there should be a reasonable time of guaranteed exclusivity that is preserved regardless of the regulatory process. The heart, from the pharmaceutical industry's side, of Hatch-Waxman, the good part of it, was intended to do. I think that is sound policy because it gets drugs made. If you cannot recoup the investment, drugs are not going to happen. That is just the bottom line. The last time a nonprofit made a major drug was . . . never. So it has got to happen. But I think twenty years is a long time in today's technology base. I think that it is something that, again, is a matter of just patent law in general. We may want to look at it as a matter of public policy, but still, guarantee enough time to recoup the $500 million investment on the drug. (*laughter*)

Q: *AUDIENCE*:

I take a little bit of issue with your claim that you're not really able to say or not really able to tailor patent length to a set of circumstances. Economists looking at patent policy will say that one size really does not fit all, and there are things that economics can say, about how patents should being assigned. That being said, I think there are real problems in terms of political economy that once we sort of open the box to giving out special provisions to different people, it would turn into a nightmare of people grabbing more than they should. I think a lot of what you are saying about Hatch-Waxman seems to be a consequence of this political economy problem. How do you – maybe this is just Pollyannish – but is there a way to depoliticize the process in a way that brings some sort of systematic thinking about how to fine-tune the system without pollution by special interests pushing for their own interests?

A: *PROFESSOR RAI*:

If I could just respond to that quickly, I did not mean to suggest that it was not clear that patents were more important in some industries than others. I think that is very clear. All I was meaning to suggest with respect to the economic literature was that, as far as I know – and you should certainly inform me to the contrary if I am wrong – we do not really have a good sense

of what the absolute number should be in any given industry. We know in some industries it is more important, we know the deltas, but we do not know the absolute numbers necessarily. That is all I would like to say. The political economy question, I think, is fascinating. It is a question that I think about also in the health care industry, which has some of the same problems as the various areas of intellectual property in terms of political economy problems. Also, I think there are comparative institutional problems to any approach you could come up with, and there are trade problems as well.