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Future of Innovation in Medicine: Incentives for New Medical Treatments and Global Health

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FUTURE OF INNOVATION IN MEDICINE: INCENTIVES FOR NEW MEDICAL TREATMENTS AND GLOBAL HEALTH

University of Washington School of Law,
Thursday and Friday, December 3 and 4, 2015

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WELCOME AND KEYNOTE REMARKS

Introduction:

Hon. Professor Sir Robin Jacob (ret.), *University College London (London, UK)*.
Prof. Patricia Kuszler, *Vice Dean and Director, Health Law. University of Washington School of Law (Seattle, WA, 7 USA)*.
Prof. Graham Russell, *Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), Oxford University (Oxford, UK)*.
Prof. Mary-Claire King, *Genome Sciences and of Medicine (Medical Genetics), University of Washington (Seattle, WA, USA)*.

PROFESSOR TAKENAKA: Good morning. My name is Toshiko Takenaka. I'm a professor at the University of Washington as well as was co-director of Center for Advanced Study and Research on intellectual property. I retired from directorship. I was a director 22 years. I feel it's a time to focus more on research and writing so therefore at this doctor conference I will be learning on behalf of University of Washington, but I am very excited with this opportunity because this will be a great success and there was such an important topic for innovation.

Usually, you know, my science background is science, computer science, and this is rather an important area, but because of my partner, Professor Sir Robin Jacob, we are able to host a list of very distinguished speakers from pharma industry as well as life science industry.

So without any delay, I would like to ask Professor Sir Robin Jacob.

[Applause]

SIR ROBIN JACOB: Good morning, you all. It's not easy helping run a conference from London when the conference is going to be in Seattle but it's been well worth it and the Seattle team have been superb. And so with a bit of luck we're going to make this one work.

The subject matter is probably the most important subject matter I think I've been involved in which is what happens when the patent system fails, when there is no patent incentive, when there is no other incentive, what happens to research? And we're going to have a vivid example at the beginning and we're going to have many other examples. And I don't think people really realize what a serious problem this is. Let me just give you a few numbers which my research has dug out. I don't suppose they're all that precise.

Big Pharma, top 20, 30 companies, spend about \$120 billion a year on research and development. Governments, charities, Gates Foundation, Malcolm Foundation, other smaller charities, between them 30 billion. You can -- NIH here and the MRC in England, and of course a lot of their money goes off to fundamental research which just leads to Nobel prize winners and inventions 20 years later.

So who is going to do the clinical trials to research new uses for established medicines? Some of this conference will be concerned with various ways of trying to get patents, and if you get them, how effective they are. And that's interesting in its own way, but it's actually, I won't say we shouldn't be doing it, but it's actually a bit of a side show, because very often these new uses cannot be patented in any way for the obvious and simple reason that how does anybody come across the possibility of a beneficial use of an existing medicine?

Why? Because doctors are treating patients. They're treating the patients for the old disease and they notice something. Few of the patients have other conditions and it's being affected, beneficially. So what do they do? They write a paper about it. That's what doctors do. No reason why they shouldn't. Only you can't get any kind of patent after that.

The regulatory system provides some sort of controls, but again, you've got the real problem, what about the generic company that's busy making the old product for the old use and lo and behold somebody finds a new use? Can you charge more for it? How does that work? That's the subject matter of this conference and it's such a serious subject that, as I say, I don't think I've ever seen anything quite as important. It's strange that it's not been tackled before, but it's becoming more and more acute and maybe that's why it's come up now.

It came up originally because of a conference suggested by Novartis and joined in by Teva, and on this occasion on opposite sides of the table. Teva is a bit of a mixed company, hardly innovative and hardly generic. Fair enough. So is Novartis, as a matter of fact, with its subsidiary. But if you're making a product Teva says, Well, no, we don't mind doing some research. The products we will be making, who's going to pay us? How is that going to work?

So they jointly picked this idea up and we ran a conference a few years back, a small one. This is a bigger one. I think I would like to see this become a bigger subject in the world in challenging people, governments, policymakers and say, Look, what are you going to do about it? Because if you don't, you will be kindly worse off.

If you would be kind enough to look at Page 28 of your brochure you will see the people who made this financially possible. Not one of these people are putting this money in order to get more out. Yes, their names are there and their names should be there but their names are there because they are equally concerned with this problem. Thank you all the sponsors.

One other little thing, all the mobiles off, cell phones is what I believe you call them in America. In court when they used to go off I used to call them cell phones as well. Are you there?

Anyway, let's get going because time is short. Every speaker is under an edict not to overrun. It would be very embarrassing if they do. They will get cut short by their respective moderators. Thank you all for coming.

[Applause]

TOSHIKO TAKENAKA: Thank you very much. Next speaker is a moderator for the key note session, Professor Patricia Kuszler is Vice Dean of the University of Washington. She will also make a short remark on behalf of the University of Washington too.

PATRICIA KUSZLER: Thank you, Toshiko. On behalf of our dean, Kellye Testy, and our entire law school, I want to welcome you all here today to this wonderful conference. It is my distinct pleasure and honor to be able to introduce our two keynote speakers and then subsequent to that I will introduce the moderator for the question and answer session which will follow.

We have two distinguished speakers today to kick off this conference. First we have Dr. Mary-Claire King who is the American Cancer Society professor here -- of medicine and genetics here at the University of Washington. Dr. King has a distinguished and long record in the world of genetic science. She is world renowned for her discovery of the BRCA1 gene and its linkage to breast cancer. She has a rich history in working with forensic genetics in the context of the disappeared and in human rights violations. Today she will be talking a little bit about personalized medicine and the movement of genetic science into the world of global health. It is -- it is an amazing opportunity for us all to hear her speak.

She will be followed by Professor Graham Russell who is at Oxford University, and he too is a distinguished scientist with a leading -- who has led in the field of bisphosphonates and their linkage to bone disorders. He will be talking a bit today about the issues that come up in the context of new uses for existing drugs which sort of takes us into the area that Sir Robin just spoke of the patenting conundrum.

So, without further ado, let me bring up Professor Russell first to speak and then we will follow on with Professor King.

GRAHAM RUSSELL: Good morning, everyone. It's a rare thing for a gentleman to go before the ladies if he's British, but that's the way they had it in the program so I hope you'll forgive us for inverting the talks. I think I'm really the warmup act. I'm not a lawyer. I'm a physician scientist. As you heard, I was involved in the discovery of bisphosphonate drugs and everything that's followed, and although there have been enormous successes, there's also been a lot of frustrations along the way. Not just related to patents, but partly influenced by patents and the way pharma companies handle drugs.

So, I'm going to start here. And the reason I'm here is that this gentleman (Sir Robin Jacob) presided at a high court case in London when alendronate or Fosamax was being challenged by generics, and he left a lasting impression on me and reading his summing up was a lesson in the English language.

Along the way during that case he managed to entertain us and mentioned that he was also a fellow of the same college (St. Peter's) as I was in Oxford, but before we pass on from this, I bring to your attention his book here. It's called "IP and other things". I'm trying to get him to sign it and to bring it with me is probably the best way. There's five copies left on Amazon if you check. I don't think it's been remaindered yet.

So, this is where I come from. I work between Oxford and Sheffield and have been director of institutes mainly devoted to musculoskeletal disease. The Oxford group is big and we have two research centers. One is the Kennedy which is where the anti-TNF antibodies were developed and

they've recently moved their 200 people from London to Oxford so we have a very big activity there now in musculoskeletal diseases which is going to be the main theme of what I talk about.

Before that, when we get into new uses for existing drugs, we have of course many examples and here are just a few that you can quickly find, and I think it illustrates Robin's point very nicely that drugs that start with one use can be found to have another property which makes them even more valuable in medicine. Thalidomide of course was a medical disaster but the drug is now very useful for treating leprosy, and myeloma.

Finasteride for the men here moved from treating prostate problems to working on male baldness. Viagra, we all know about, it started as an antihypertensive drug, and aspirin of course, one of our oldest drugs, started as a painkiller but has been found to have more and more effects important in cardiovascular disease prevention, and possibly in cancer prevention.

So, we have an issue, new tricks, new purposing, new uses for existing drugs, they all mean more or less the same thing. Folks like some names better than others. So, one of the things that's currently of interest, and I'll perhaps illustrate some of the difficulties here, is life span extension. Do you all want to live to be 120? Hands up. Maybe not. But it's interesting how the study of aging mechanisms has uncovered a number of old drugs which have remarkable effects on stem cell survival and even survival in animal models. Metformin is one of them, a diabetes drug, Rapamycin which is an immunosuppressant drug also has similar effects. And even the bisphosphonates, which you have mentioned, they're bone drugs but they and I'll end up with this theme, have anti-aging properties and effects on DNA repair.

And of course, I can't get away having mixed with lawyers to know that there are drugs like Pregabalin that you get very excited about and seem to spend enormous amounts of time working on.

So, musculoskeletal diseases, you're probably are aware of these problems. One question I could ask is: How many people here have a near relative or old friend who's had a hip fracture, for example? It affects most families. Not many hands but probably think about it and more hands will go up.

So, musculoskeletal diseases are among the commonest diseases and we have the very common ones that you see here, osteoporosis, osteoarthritis and so on. Cancer affecting bone, an important topic. And we have an enormous number of rare inherited diseases, over 450 in the musculoskeletal area for which there are mostly no treatments, but in one or two cases emerging treatments. Great cost associated with them, and slightly different regulatory paths, which is an interesting topic in its own right.

Just to give you an idea of the prevalence of musculoskeletal diseases here is one depiction of it showing that approximately half of adults have something in the musculoskeletal area going on. How many of you have back pain, not necessarily today but in the last year and so on? And arguably, it's more important in general practice than conditions like heart disease and pulmonary conditions. And of course, many of these diseases or disorders affect the elderly and we have an aging population and there's lots of these. The queen's run out of telegrams. She can't send a telegram every time somebody reaches 100 anymore, at least I don't think that's happened yet but it's likely to happen. Many, many more people reaching 100. And of course, that's projected in terms of sheer numbers to become much greater and the health burden is of course enormous. Alzheimer's particularly a huge problem.

If we go back to the osteoporosis theme, osteoporosis is essentially thinning of bones that lead to fractures, and fractures are common, and hip fractures in particular are devastating. They're

often the last medical event in an old person's life. They have a fracture. They go to bed and they never get back to an independent life.

The prevalent figures are huge. One in two women, one in five men after the age of 50 will have a fracture in their remaining lifetime. Should we be trying to prevent fractures in all those people or just selecting the ones that we might do a better job in? And of course, it's only relatively recently, last 20 years or so, that we've had specific treatments to try and reduce fracture rates. So, bisphosphonates dominate this but of course the start was in the use of estrogens. After the menopause bone loss occurs in women, an estrogen was one way of ameliorating menopausal symptoms but also reducing bone loss.

Estrogen developed a bad reputation in terms of causing breast cancer and possibly heart attacks and went out of favor and this encouraged pharmaceutical companies and scientists to develop estrogen-like drugs which would have good effects but not the bad effects. And this is what that looks like. You can design estrogen like compounds that work on the estrogen receptor that have good effects on bone and the heart and avoid the bad effects of estrogen in terms of causing breast cancer or uterine stimulation and tumors in the uterus.

Many, many such compounds have been made and of course patented and these are called SERMS (Selective Estrogen Receptor Modulators), there's some examples shown here. In general, this hasn't been a particularly successful field; there have been many more failures in drug development than there have successes. And of this list only Raloxifene which is a Lilly drug, and Bazedoxifene which was originally a Wyeth drug and became a Pfizer drug, more of that later in corporate cannibalism, have been registered for use in osteoporosis. They're moderately successful but they're not as good as the best drugs we have.

And just very quickly, this shows you the profile, for example, of an estrogen like improved estrogen, selective estrogen receptor modulator Raloxifene compared with estrogen, and you see as you look at the bone, breast, uterus, cardiovascular, brain, that Raloxifene has the good effects and avoids the bad ones of estrogen.

Just a word on Raloxifene itself. This illustrates the issue of patents extraordinarily well and it was one of my first encounters with the patent world. It's an Eli Lilly drug, a wonderful man called John Termine left NIH to go to Lilly as their head of science for musculoskeletal and female health problems and he found that they had this thing stuck on the shelf which had been developed as an anti-breast cancer drug like Tamoxifen but it had failed in initial trials, which were actually extremely badly done because they were in patients who were in a terminal state when you wouldn't expect to see much, but it was sitting there languishing and he thought, well, let's see what it does to bone. And they developed it and patented it and it is used in osteoporosis.

But the patents for Raloxifene were challenged largely on the basis that one of the cancer scientists had done a bone study which was extremely poorly done but it was quoted as showing the beneficial effect on bone. The data didn't add up, the stats were wrong, but that brought down the patent in some territories. And this litigation ran for at least 10 years, and I know there are people here who are involved or have been involved in that. And I think this is a good illustration of what happens to an old drug which is reused for a new indication with great chances of success but then gets constantly challenged by generic companies and the company has mixed feelings about how hard they should continue in that area. Lilly tried to develop a follow-up which didn't actually work too well because of side effects.

So, bisphosphonates are the major drugs used in treating bone diseases at this point. There's a lovely background story and I've written about this and I think that will be among your materials, but basically Procter & Gamble were trying to develop water softeners and they made these stable

phosphorous compounds which stopped calcium carbonate deposition in water systems. You can still find these sorts of compounds in dishwasher detergents and so on, but the structure of the PCP, as you see down in the bottom here, is an extremely stable chemical structure and these are the things that became drugs. And they started as drugs we thought because they blocked mineral exit from bone but it turned out that they have a very specific enzyme action in the so-called mevlonic pathway of cholesterol metabolism.

And that observation wasn't patented by the universities because they didn't see much point in patenting that and how would you actually ever commercialize it? But we now understand how these drugs work and they're very statin-like in some respects, and I'll come to that theme in just a moment.

So, this is another story that some of the older drugs are developed without mechanisms of action actually being known, mechanisms get known and that opens the way to exploiting new medical uses based on the now refined mechanism of action. Vast literature, 20,000 plus publications on biphosphonates in PubMed.

So, there are lots of bisphosphonates, there are about a dozen that have been used in clinical practice and they're shown here. Their key properties are that they bind to bone very avidly.

If you make them fluorescent you can actually see them stick on bone surfaces. This is probably the only cell I'll introduce to you, but this is the osteoclast, the chomping cell in bone that dissolves bone and bisphosphonates get in and mess up the machinery of that cell. And you can see here if you use a fluorescent bisphosphonate it is actually going inside the cell.

And one of the first uses of bisphosphonates was as bone scanning agents. You could link them to radioactive technetium and light up lesions of high bone turnover like in people with breast metastases. And there's some lovely illustrations of this. As you see here, these are modern imaging approaches where you can very precisely tell where somebody has a metastases, based on the bisphosphonates localizing to that site and having an external readout.

There are many diseases of excess bone loss, not just osteoporosis but also arthritis, effects of steroids, effects of attempts to reduce androgens and estrogens in the treatment of cancer, for example, and bone cancer metastases themselves, and particularly myeloma which is a horrible condition to have and causes fast erosion of the skeleton.

The major uses of bisphosphonates are in osteoporosis to prevent fractures and in oncology to prevent the skeletal complications that come along with myeloma or cancers. And this is a summary, very pictorially, of the major bisphosphonates used to prevent fractures in osteoporosis. In general, they reduce fractures by up to 70 percent so they're remarkably effective. You can reduce hip fractures by about 40 to 50 percent if people take the drugs. And that's of course where the IV drugs have an advantage because it's veterinarian to infuse a drug if a patient can't get away, whereas if you give them by mouth they tend to forget to take them.

Fosamax was the one where I came across Robin Jacob first which was contested by the generics on the grounds that it was actually an old chemical, which it was, which was possibly predicted to have biological effects. But these are the drugs that made it. They all became blockbusters in terms of the billion dollar plus markets.

There are some remarkable properties and I pick out zoledronic acid or zoledronate as being quite different from the others. It's actually the one that is injected, but you only need to give it once a year, five milligrams once a year, and it reduces your bone loss continuously throughout a year. And in fact, people have now stopped bothering to get the second and third year infusions, because they find that three years after one infusion it's still working. So this is veterinary practice

at its best. You give one infusion and you can actually send the patient away for maybe a couple or three years. It's great for compliance.

The biggest use of zoledronate has been in cancer, and just to show you illustrations of what you are trying to accomplish, here are metastases from breast cancer. Here is a skull, "pepper pot" skull with lots and lots of holes in it from myeloma, and this is what you try to prevent.

Now, it's interesting and related to patents and also commerce that the two oral osteoporosis drugs, alendronate and risedronate, were never developed for treating cancer. They could have been. They would have been orally active and that seems like a missed opportunity.

But in spite of all this apparent success in osteoporosis itself, the use of drugs appears to be plateauing or even declining and it's a mystery as to why that should be because there are more and more people who might benefit from osteoporosis treatment and some of the reasons are given here; that now they're generic. We no longer have the pharma industry advertising and advocating the use of drugs, providing education to physicians and so on. And another factor is that very rare side effects have made better news stories than good news stories about benefits and there's been a huge rumpus about very rare side effects and lots of litigation associated with osteoporosis of the jaw and atypical fractures.

Are there new opportunities for osteoporosis drugs? Alendronate now costs less than \$20 a year for treatment so why would you spend a billion dollars developing a new osteoporosis drug? osteoporosis drug? Well, there are some stalwarts out there who continue, and there are two coming along, one is a cathepsin K inhibitor from Merck which probably cost the proverbial billion dollars to develop and the other is an antibody to a protein called sclerostin. Both of these are derived from studying rare diseases, understanding the mechanism and then devising a therapy based on that.

We can make new bisphosphonates. We can design them very selectively knowing the mechanism of action. No one is interested in developing them. We have supremely powerful ones but no Big Pharma wants to take them on because the marketplace is saturated with generic drugs.

So back to the theme of where next? And with bisphosphonates in particular there are a number of observations that could lead to new medical uses which are difficult to patent and difficult to commercialize. And among these I would list rheumatoid arthritis bone loss, prevention of colon cancer, enhanced DNA repair and life span effects, and I'll illustrate each of those very briefly. There's of course a much longer list of things that have never been done but could be done including even effects on malaria and leishmaniasis. We're in Gates territory here. These drugs are supremely active on protozoan parasites. You have a problem in how you deliver them but they are one of the drug classes that could be used.

So zoledronate, just to illustrate the point about what might have been done but wasn't done, this is the Novartis drug, it's an amazing drug, as I just showed you, for its longevity of action. It was never developed for indications like bone loss in rheumatoid arthritis. Why does that matter? Because actually in arthritis, particularly in rheumatoid arthritis, loss of bone is the first step to leading to deformity. We don't see patients like this anymore but if you don't treat rheumatoid arthritis, you can end up with that degree of deformity and the prediction is if you can control the inflammation and the bone loss you can prevent that. The reason it wasn't developed is that it came along too late in the life cycle to be commercially worthwhile to actually do the studies before the patent ran out.

The generalization is that bisphosphonates have never been properly assessed in rheumatoid arthritis.

So a few more illustrations on the theme of old dogs and new tricks. I've already suggested that there might be three areas of bisphosphonate use which won't be commercialized but will probably have to be pursued outside the pharma sector. The first is reduction in colon cancers. I'm not going to go through all the data but in people taking bisphosphonates, they have a 40 percent lower occurrence of colon cancer death, amazing.

In the hip fracture studies done with zoledronate, after three years there was a 28 percent reduction in death rate in those getting zoledronate. The reasons are not totally clear, possibly cardiovascular, and there are in fact studies in rheumatoid arthritis populations who are particularly prone to cardiovascular disease showing that if you take people on bisphosphonates you can see a 28 percent reduction in heart attacks. These are all potentially very important medical applications.

If we want to live longer, we have a wonderful mouse model where you combine statins and bisphosphonates in a model of premature aging and you double the life span of mice. These mice actually have the equivalent of a human condition called Hutchinson-Gilford progeria syndrome. This is where people at age 10 look as though they're 70 and there are studies going on using statins and bisphosphonates together.

A couple of points to end up with: I've talked mostly about drugs but of course living among orthopedic colleagues who vastly outnumber us, I think we have 50 orthopedic surgeons in our place, we know that implants and artificial joints achieve miracles for patients without drugs, and of course this is an area for invention and patents and generic intrusion.

The problem with implants are that they don't go through the same sort of process of evaluation and they can run into difficulties if they don't work too well. There is actually even an Oxford knee which is very successful, just a one compartment knee replacement.

This has transformed the lives of many people. I heard a story only this week of somebody who had two new knees and a new hip. He was working as a decorator and he said that probably in the old days he would have been confined to bed, or be dead already, if he hadn't had new knees and hips.

I'm sure we're going to hear a lot about drug development, but basically it's an extraordinarily long process and it's extraordinarily costly and there's a lot of awareness that maybe pharma is getting less good at it. The investment goes up, but the outcome in terms of good new drugs is not going up.

Mergers aren't necessarily the solution. I was given this slide by a friend which I thought was somewhat amusing in the era of commercial linkups, actually combining big companies. One thing it does for drug discovery is to prune out some of the activities and to narrow the number of projects that people work on, but these are apparently the sort of figures that show that the net market value of the combined companies goes down.

In my own experience, risedronate, one of the very successful oral bisphosphonates is a victim of corporate takeovers. In the last I think about seven years risedronate went from Procter & Gamble to Warner Chilcott, thereby saving huge amounts of tax because Warner Chilcott was based in Ireland, then to Actavis, then to Allergan and now they're merging with Pfizer, again to go to Ireland and save tax it seems.

A final thought: There are some people so fed up with the industry model of drug discovery and its huge cost and the fact that many companies work on similar targets and don't share their data and the rest of it, that there's a big initiative to do open domain research where you don't patent discoveries at all, you just make them freely available to the public. The Human Genome Project was one great example of success there, and in Oxford we have one of the branches of the

Structural Genomics Consortium run by Chas Bountra who is a very impressive guy, and they set out first of all to do human protein structures.

A lot of pharma industries have invested in these activities just to increase knowledge. And they've made crystals and elucidated structures of 1500 human proteins which are potential drug targets and released them to the public domain and they screen chemicals looking for potential drug templates which they then hand back to the industry to develop. It's a model and these folks are passionate about it.

So drug discovery is not easy. I'm on the one-minute signal. This is a bit like the reserve coming on here.

And the modern approach is to identify targets, work on them, but we mustn't forget the role of chance, serendipity, luck and particularly championship. If you're an emerging company and you want to keep your drug going, you have got to be pretty loudly spoken and heard.

The trends, we're going to hear a lot about this, rare and orphan diseases have regulatory routes that may favor introduction of new medicines for conditions that wouldn't otherwise be worked on, and of course personalized medicine. And I suppose our challenge is can we make these road signs obsolete. Now, this road sign has a lady following a gentleman. She probably has osteoporosis based on her stoop. He probably has osteoarthritis based on his posture and also the fact that he has a walking stick, but the world doesn't change. She's actually picking his pocket. Thank you.

[Applause.]

A. Commentary on Keynote Address and Challenges in Incentivizing Development of New Treatments and Drugs

Moderator:

Laetitia Benard, *Allen & Overy (Paris, France)*.

Panelists:

Dr. Joerg Thomaier, *Bayer A.G. (Monheim am Rhein, Germany)*.

Professor Graham Russell, *NDORMS, Oxford University (Oxford, UK)*.

Professor Mary-Claire King, *Genome Sciences and of Medicine (Medical Genetics) (Seattle, WA, USA)*.

Ilana Odess, *Woven Orthopedic Technologies (Manchester, CT, USA)*.

PATRICIA KUSZLER: Well, thank you for both of these wonderful talks on compelling issues in healthcare and in the world of translating research into clinical medicine. So we now have a brief question and answer session that will be chaired by Laetitia Benard who is the lead -- leads the IP practice in the Paris office of Allen & Overy. Also joining us on the panel will be Ilana Odess who has a long career focused on entrepreneurship. She is with Woven Orthopedic Technologies of Connecticut. And Dr. Joerg Thomaier, Dr. Joerg Thomaier who is a distinguished IP attorney from EU and heads the Bayer Group. So perhaps you can all come forward.

MS. BENARD: Hello, everyone. So I have the pleasure of moderating this panel today and I will start by introducing two new speakers, Dr. Joerg Thomaier and Ms. Ilana Odess. Dr. Joerg Thomaier has a Ph.D. in science and he is a qualified European patent attorney. He joined Bayer's patent department in 1997 and he has been chief IP counsel of Bayer since 2010,

responsible for all IP matters at Bayer. Today Dr. Thomaier will talk about efforts and financing in pharmaceutical innovation.

Mrs. Odess has spent her entire career within the healthcare and life science industry. She has held seniority positions in large pharmaceutical groups but also with start-ups and she is an expert in leading companies from concept to clinical application.

MS. ODESS: Good morning. It's a pleasure being here in Seattle. My name is Ilana Odess. I started my career actually at Johnson & Johnson, worked through three continents, Israel, later on in Europe and then in the headquarters in New Jersey. After eight years, I started my first company in the Bay Area in the cardiovascular space that was sold to Boston Scientific. In a nutshell I have experience with small companies, large multi-international companies, have been on the operational side but also on the investment side and the financial side.

So today I have three objectives: I want to make this talk very practical to the audience and I want to prove that funding is actually available if you have a good idea, but more than that, if you have a company. No. 2, if you could identify the right investors for you, and the third, you have to demonstrate how you could be successful.

So here I'm bringing some data from Pricewaterhouse and Coopers. Actually the last quarter, the third quarter of this year has been a phenomenal quarter, probably the best in the last 20 years for the life science. And when I mean life science, I mean biotech as well as med tech. There has been \$2.9 billion invested in Q3 of this year in the life science. Out of that 2.1 in the biotech. So around 194 companies received funding. The volumes have been actually remaining flat which means that every deal got more money. The average per deal was around \$14.9 million for an investment. So that's good news.

Regarding early stage companies versus late stage, it has been always known that you first have to get your IP, have clinical studies and then you could go to big VCs. In the latest reports and trends of this year, we could see that a lot of the investments actually are going to early stage companies, more than 50 percent, which is very essential. It's -- about 1.8 billion out of that 2.9 that I mentioned is going to early stage. In number of companies, 87 transactions in the biotech have been early stage companies.

So it is indeed a great time to be entrepreneur right here in the United States. So how do you identify the right investors? Again, I mapped out here all these investors that you could go. I won't go into detail but I'll give some examples. Governments are very active today so you have in the U.S.A. SBIR grants. You have in Israel incubators that are supported and sponsored by the chief science officer. There are over 20 incubators. Some of the big companies also sponsor them, though on the government and state side there's a lot to be done. A state like Ohio puts in about \$3.9 billion in startups. If you take example like Cleveland Clinic, and that's under the hospitals that you see here, they have a supporting system for startups. So a lot could be said for that.

Regarding insurance companies, under the buying groups, if you look today, I'm based in Hartford, Connecticut where the insurance companies are, you'll see that they opened VC arms and investment arms. If you look at Aetna, Aetna today has a VC arm and other ones as well. So there's a lot of opportunities to raise money by those groups.

So how would an entrepreneur here in the audience that may have IP start a company and identify what's right for him? First of all, the right industry. You won't go to a body that only does software or greentech, et cetera. You'll go to someone that actually supports and invests life science. The second thing, identify where you are in your life cycle, and I'll show that later on. In every life cycle you have more appropriate bodies that will invest and the likelihood will increase versus other cycles.

Region is very important. If you look in detail, the regions that are usually supported financially are the ones on the coast. So Boston today is a leader in the biotech and med tech industries. San Francisco, Seattle has its efforts and investment room as well. So being in the right location on the coast actually will give a lot of supporting from the investment groups.

And here is a depicting image again how you would map it out. If you want to go to high net worth individuals, identify who's right for you. The same with angel groups, VC funds, corporate VCs, et cetera. You can go to all of them. It takes a lot of effort and time to do funding so really allocate and map out what's right for you.

Here is a very interesting slide that really is important to understand. Again, every stage, if you're in the feasibility stage versus a Phase 1 or 2, you'll have a different investment or potential investment. So very early could be government like the SBIR grant, the incubator, we gave examples. Later on you definitely could go to VCs, private equity or strategics, the pharma companies or the med tech companies. The longer you are in this process and the more proof that you go from Phase I, II to III, obviously the more likelihood of commercialization you will have and the more royalties you will get so a very encouraging slide.

How could you be successful? First of all, every investor, the first question they ask, does a company mitigate their risk? Do they understand the risk factors and how do they mitigate them? The second question, which is not less important, is, what will my returns be like? Am I going to return two times on my investment? Will I lose my investment? Very essential discussions.

So this is a talk that I gave actually in Yale in the MBA program and I really believe that there are five components to make a startup successful and mitigate those risks. I'll go through only three today due to time. First of all, it's filling a need. Filling a need is very important. It's not only about getting your IP but does your IP address a medical need, a medical unmet need. And here are actually some technologies, four of them that come from Israel that really addressed an unmet medical need. For instance, Argo Medical, okay? Restores mobility in upright mobility with people that can't walk.

Given Imaging that was sold later on, it's an important company that took a camera, miniaturized it and basically could look at the digestive system. There are other examples obviously from other industries but I focused on that.

So developing a plan is very essential. And again here, I mention IP as a sector, an important factor, but it has to work in tandem and conjunction with many other aspects of building a company and those aspects could be the regulatory approach like FDA. If you have great IP but the product has never been commercialized because there's not FDA approval, you will not get the funding.

Other important things are reimbursements. Do you have the buying groups behind you? Will you get a reimbursement code, specifically if it's a new drug compound or new treatment? So all these six elements have to work together and most important is, Does the product, is it really covered by the IP?

Develop a plan. Why is that important? No. 1, it aligns all the management to be focused on the near term milestones. No. 2, you really get the resources of the funding and you allocate it. For instance, in Woven Orthopedic Technology, \$0.70 on the dollar goes to R&D. That's what I promised my investors and that's what I actually do. We have audited numbers; our investors can see it. So what I'm saying is this mitigates the risk to the investor and restores confidence that the management team is focused and they have near future milestones.

Another important thing is, who are your customers? In today's world it's not just the patient or the physician. Actually the way we see it is there are five relevant, they all start with P: The

provider, the physician, the patient, the payer and the policy maker. Make sure that your company has a strategy that addresses all of them, okay. The policy maker, for instance, how will you get that same reimbursement code?

Another important thing is, what do you need in long term in capital raising? For instance, we're raising Series A, but my investor in Series A wants to know how much he will be diluted in the next five years. When is my inflexion point? How much will I raise throughout the lifetime of the company until profitability? So you have to have not only a near future plan but a long-term plan.

Build the best team. Again, I bring here Apple as an example. When Steve Jobs came in in 2000 he turned a company that had 1 percent of the market share to the No. 1 market cap with 500 billion over a decade. It takes time. Same thing as what I did in Woven. I took the No. 1 surgeons, trauma and orthopedic surgeons, spine surgeons to be on my board. They understand the meaning of fracture fixation and the lack of a medical solution today with the fracture fixation.

Then I took industry people. I took the main people that worked in Synthes, a company that was sold for \$21 billion to Johnson & Johnson in 2012 and was the largest transaction ever in the history of orthopedics and I made them the chief technology officer in our company, the chief legal officer and the chief medical officer. So knowledge of the market is very important. No. 3, I added to the board members the No. 1 distributed Medtronic spine that sells more screws than anyone and understands that there is a problem in older population with screw fixation due to the lack of the quality of the bone.

So this is my last slide. I'm being rushed here but I want to say one message. Even in funding, you need to be creative. If usually there was known to be debt and equity, be creative. There also are hybrid situations. For instance, in Woven when I started the company two years ago, I had no money. I needed immediately money and I did a convertible debt note that was mandatory converted so they got a 15 percent discount on the Series A that happened three, four months later, and within 10 business days I raised \$650,000. So really, you can get creative in structures.

A main message that I would like to say is that "no" is always "yes" with conditions. So if you're thrown out of the room and someone says, no way, this is so early, it's only idea, only IP, he actually means, yes, but you have to find the right way, the right conditions to make this happen.

So in summary, I think this is a very optimistic statement. There has never been so much funding available for early stage companies, specifically in the life science. Very encouraging statement. You have to take this as a strategy in identifying the right investor and the right place. You have to have a solid plan, long-term, short-term of course, and you really have to have leadership in it. Be creative. Don't take no for an answer. I will be around if anyone wants any questions. And again, thank you for having me.

[Applause.]

DR. THOMAIER: Okay. It's me. I am Joerg Thomaier, head of IP Bayer, already nicely introduced by Laetitia. For the sake of time, this is short so don't worry, yeah, maybe 12 slides but it's short. So...

The other one to pick up on my colleague on financing. Because there's money around to get and we already talked about mitigating it, risks in it and then a business plan to get the money. So let's go into what's happening if you are talking about business case or research and pharma. Graham already in his speech indicated, talking the drop down of ideas when you start developing compounds. So this is from U.S. pharma from 2010, I think the figure is originally.

So if you start with about 10,000 compounds at the beginning and you work on it and you try to develop it and you go into the preclinical phase of your first test if it is really effective, you're dropping down to about 250. When you enter in clinical trials you're already down to five and until you're on the market you're at one, one out of 10,000.

In 2010, the numbers were on average about one billion. Believe me, it's getting more expensive and that's maybe one thing which I want to address what Graham just said when he said the expense, the moneys, companies like us are spending on the research going up but the number of proved compounds are not going up. One of the reasons for sure is that the money you have to spend per compound is getting up heavily because we as a society request much more regulatory data, for example, which costs more money. Which is okay because we want to have safe drugs, but it just costs more money. And if the money you spend is let's say kind of restricted, you can only develop a few less projects because each project is more expensive.

In saying that, I'm happy being with Bayer because the last two or three years we launched more new products as ever in our history before in the time frame. So obviously we were lucky, I mean, of course very professional in selecting the right compounds, but that's -- overall on the industry, this is really the problem, that you have to spend much more per compound. And one billion I think -- and I know it's not enough anymore. So one of our actual top compounds, for example, Xarelto, a blood thinner you may have heard, oral anticoagulant, already consumed about 2 billion in development costs together with our partner Johnson & Johnson. So it's quite some money you put in there.

And these are the uncertainties. I mean even Phase III, shortly before you really fight for approval, your compound can get lost and then you've already spend a couple of hundred million on the compound when it's dying. So these are the risks you have in this kind of industry and if you talk about mitigation or how you safeguard to get the return, you are pretty easy and quickly on the topic of IP so talking about patents. That's the typical picture, if you the compare patent product and commodities.

Now, if you take an unpatented commodity and you launch it into the market, of course you work in the market. You build up the market. Your turn of work gets to a certain height and then you come to kind of an equilibrium with the competition where you have a plateau in the turn for the grant. That's the blue one. Now take a patent that's an innovative drug, it's the red one. It's steeper because it's higher. I mean, if it's really innovative and has some respect, it's steeper, it's very well received by the market. You get up in high levels, much higher than unpatents because the patent provides you with a monopoly. You get a lot of money, but what is important is at the very end when you see -- you see these steep downturns after patent expiry, so if you have a drug you lose -- within a half a year you can lose up to 80 percent of your business with such a drug.

So this -- because competition gets in, generics gets in, they don't have to spend the research money, they "only" do have the manufacturer costs but they sell much cheaper. You are out of business. So that's the time frame, that's the insurance you have to get the money, the investment back. That's why the investors, and correct me if I'm wrong, but still are asking these kind of companies, do you have kind of IP protection to safeguard that you really can get the benefits of your great, great ideas?

So without the IP protection you see the price collapse. So if you want to fund these expensive kind of research, and it's getting more and more expensive, it's not only the research, it's really a large part is the development cost, so this is nothing which companies or research or science needs you to do, this is our safeguarding. This is our -- as a society we should have safe drugs. We should have regulatory data which eats up most of the money. Which is fine but needs

to be just realized and accepted that this is money you also have to gain with your drug to spend with the next development.

Just a bit about Bayer. We have three -- four sides where we do basically the healthcare research. And we spend actually last year 2.3 billion Euro in research in health. Just on something more this year, even more next year because we're going to grow this budget. We have about 8,000 people working in R&D and about 11 percent roughly of our turnover in this area.

What are my conclusions? On the way to the market, okay, we have large up-front payments as in front-loaded investment. It means to get the money back at the very end and the probability of success is let's say restricted. Because I mean most -- and that's really the message I want to send in the first slide, very, very most of the compounds you're trying to bring to the market will fail. Because I mean we are human bodies and biology is very sensitive to everything you bring in so the probability that a drug, be it large compound, be it a small chemical compound, will have some effects, yeah. And most will not have the effect you like so you will end up with only a few.

On the market, as soon as you are successful, of course the generic industry is keen to pick up and do their business so you will come under pressure immediately once it's possible, and therefore you need a period of protection to get your money. So therefore I think sustainability R&D -- sustainable R&D, even healthcare R&D is only feasible with IP protection to refinance the whole thing.

From a patient's point of view, you need to have sustainable healthcare R&D to get steady innovation for the benefits of you and us as patients. I mean, every one of us has I think in this large a family has someone who has certain kind of diseases and is happy to be able to treat this or yourself, so therefore this is for us from no one else, yeah. And even for the generic industry, I mean that's the basis for their business as well because they will view their pipeline and new products only if we create new products, if the industry creates these products.

So at the end I wanted to make the point, I think I did, that IP is to the heart of it and it also counts for the title of this conference of new users of old drugs or secondary mentions as they are called. Also, they need a lot of money to be funded. The research is not for free. And well, there's a big success story behind pharma and health research in the history of mankind, I think it's almost exclusively driven by pharma industry, yeah. That's something which had to be kept in mind too.

So thank you for having me. Thank you for listening and I'm always happy to have a lot of questions. Whatever you like. Thank you.

[Applause.]

MS. BENARD: Thank you very much. Any comments from our panelists or should I start with the first question? Okay.

Mrs. Odess, I think you stressed the importance for start-ups to put in place the appropriate structures right from the beginning to be sure to have the appropriate patent portfolio and the appropriate development plan in place. We all know that many start-ups may fail because they didn't put in place the appropriate structure and regulatory development plan for their product.

What kind of advice would you give to startups to put that in place and to find the appropriate support to do that?

MS. ODESS: Again IP is very important. Also Woven Orthopedic Technology, my fourth startup, started around IP. We bought the IP from a surgeon and around that we built the company. But beyond IP really you need to know that you're addressing an unmet medical need. Otherwise, this company, this idea will never grow beyond the IP so you will never get your royalty streams.

You will never be able to build it, and at the end of the day, the idea is to bring new therapy, new treatment to unmet medical needs.

And the other things that have to work with IP is, again, the regulatory, the reimbursement, quality control, compliance like the Sunshine Act. If you don't think about these things, it doesn't matter how much IP protection you have, the company will still not succeed. And again, I'm not trying to minimize the importance of IP. In Woven and the other companies that I had, I always put a big portion of dollars on IP to understand that I have the freedom to operate, understand my protection, infringement risks. So we built a lot of IP around it, but the other sectors can be deprived in funding. It's very, very important they all work together in the correlation.

MS. BENARD: And very often I think startup companies do not have the financial resources to find the appropriate support. Do you think one solution could be more partnerships between public -- I mean public entities and especially universities with startup companies?

MS. ODESS: Absolutely. So the good news, again, there's more funding this year more than ever, but having institutions, if it's hospital, university hospitals, academic, align themselves with startups, I see this as something that could really lead to more innovations, more companies, newer treatments. And it's a win-win situation if the university has obviously stake and skin in the game.

It's also important, a lot of the university have the transfer tech departments, how to work with them. It's not always easy. So finding the right way, supporting the startups and bringing it to a win-win situation I think is essential and could really, really help.

MS. BENARD: Thank you very much. Professor King and Professor Russell, can you comment maybe on your experience working with private companies on this type of partnership?

PROFESSOR RUSSELL: Well, I'm not -- my very, very limited experience of, through universities trying to patent things, is a huge diversion from what you prefer to do in academia. I see a nodding head on my left here. All universities have, you know, IP departments to protect discoveries made by their staff. Maybe in the UK we're less successful than in California, but personal experience from friends and colleagues is that it's, you know, you have to be prepared as an academic if you really want to pursue it to devote a lot of time to it.

On the positive side, there are initiatives that you were talking about and we have the Medical Research Council and the Wellcome Trust and bodies like that who have put in quite substantial funds into a development path for promising new potential drugs. think you have to wait to see how many of those succeed, and if a success rate is anything like the one in industry we won't be doing it 20 years from now.

MS. BENARD: Thank you very much. Dr. Thomaier, would you like to comment on that?

DR. THOMAIER: There's not a lot of comment. I think there's some truth in it with regard to the diagnostic field, yeah, the necessity for spending for regulatory is much lower because you're not treating the body. You're not putting a lot of stuff into the body. What you are looking at is the sequencing and you're looking at it to find the right genome. The basic knowledge you have to have is what's -- how should it look like and what's the raw mutation so that you have this kind of diagnostic. It's a completely different way to develop things, so yes, two, like I say it's -- how do you say it?

DR. THOMAIER: Apples and oranges, right.

MS. BENARD: Thank you. I have a lot of questions for you. I mean listening to all the presentations I think what is key is how to value the innovation and when you talk about financing pharmaceutical innovation I see there are two key criteria: The first one would be the duration of the exclusivity, whether it comes from patent protection or regulatory exclusivity or a combination

of both. The second key element would be the pricing of the drug. And it seems to me that we are not really very sophisticated today in our discussions with health authorities and in the mechanisms of price setting.

So what do you think about that and what is your perspective from the industry in the discussion you have with health authorities to value innovation and set the price of drugs?

DR. THOMAIER: Okay. Well, fortunately I do not have to do these negotiations. Well, I mean, it's a very difficult area. I mean from the perspective as a company as we are, as an industry, as a business, as we are, one of the perspectives of course is to make more money, yeah, we want fair pricing which means it needs to be pricing -- and you need to end up with a price that gives you enough room to make up your investment and to make an appropriate profit. Of course you're always in a tension field with public interest because as a patient, of course I would like to pay as low as possible. As a society, it's depending from how our societies are organized, so I mean if a free pricing area or you all have to pay out of your private purse, you want to get it cheap. If you're a more government driven health system, the governments don't want to pay that much.

And the problem, and we have to take care of that with the authorities is do the pricing, if there is a pricing. I mean there are still markets, I believe we are sitting in one of them, which is fairly free pricing still, is that we should not overdo, let's say, the cut down on the price, do not -- I mean otherwise you kick off the effect also of the IP which enables sustainable research, yeah, gives you the opportunity to make up the money. But it's very -- it's a field where the -- a very sensitive field because you are in very -- in an area which is very -- you have high tension.

I always say it's -- I mean I would prefer if we go to pricing, and fortunately I don't have to negotiate them, yeah. I would be happy to negotiate a price for a Porsche because no one would care how expensive the Porsche is, but if you talk about health, it's something different. We are in an ethical field and therefore both sides, you know, need to be appropriately sensitive to negotiate fair enough to fulfill the needs of both sides, therefore, authorities or the public as well as for the industry.

Otherwise, because as I said, if you look to the past and the history, it's -- the health industry was responsible for most, I think even all of, but most of the fine development and bringing new trucks and treatments on the market. Also for the medical needs out there, you should not dry it out, yeah. And that's basically what you should keep in mind.

MS. BENARD: Two weeks ago in France I heard a comment from one of the -- I mean the president of one of the health authorities in France, he was talking about the pricing of drugs and he said it's absolutely not legitimate for a company to say that when you value the innovation of one drug, you have to take it into account the failed research. So what do you think about that?

DR. THOMAIER: I mean refusing this for me, I have no other word other than this is ridiculous. Because I mean, if I start to research, as I showed on the one slide, it's similar in the oncology field and we start with 10,000 potential compounds. And 9,999 will fail during the way and one successful one. We spend a lot of money on these failed parts and you also have to get this money back, otherwise you are drying out of money --

DR. THOMAIER: Well, absolutely --

DR. THOMAIER: I'm not saying that the failed is the major majority of the spending, but it's also not negligible spending so to say you should not put that into account, that's plainly wrong.

DR. THOMAIER: It's part of it, yeah. Well, even a failed product which fails even to three and then you're in the hundreds of millions and you need to get that back too from the successful ones.

MS. ODESS: If I may comment, again, I'm not a reimbursement expert and this is a very specialized field, but again, on the medical device, we always have to have medical outcome, clinical outcome. So, for instance, the days that I was in Johnson & Johnson and we came up with the first stent, Palmaz-Schatz, we had to compare it to CABG to open heart surgery and show that we have equivalent or better results in one lesion or multiple lesions. And through a very expensive clinical study, it also had IP but we also had to go through a rigorous clinical study, with five-year follow-up, we showed that we had a better clinical outcome.

So now you could argue for the reimbursement and the reimbursements are very different in the states, in Europe and every country in Europe and every region within the country, but in the U.S., we could claim that we could take a CABG procedure that's about \$8,000 and now have something like that for stents, although again, stents were much less in those days. But it all comes to the evidence, to the clinical evidence that you could prove that you're as good or better.

In Woven Orthopedic Technologies, what we prove is that we reduce revision rates as a result of better screw fixation and that's how we're actually going to make our case for reimbursement. So it's -- again IP is important, but clinical studies are not less important to prove the clinical outcome.

PROFESSOR KUSZLER: I think we have a nice diverse group of folks on the panel and I think it would be good as long as we have 10 minutes left or so to get some questions from the audience on these excellent presentations. We've covered from diagnostic really to end marketing so perhaps some audience members have some questions? There are microphones set up so that you could come forward.

AUDIENCE MEMBER: As head of intellectual property for a pharma company. I think this conference is terrific and can address some really important questions. A fundamental issue that I think we have to recognize is the development of pharmaceuticals and even ethical reliable regulated diagnostics is that profit-driven companies are doing this. We've heard about how to get the investment. We know we need to have the investment and I think it's also important to know, while we think about recovering our sunk costs on R&D, that's not what we're doing in a pharmaceutical company. We're making money to invest in the next generation of 10,000 failures. We're not recovering anything. We've already paid for that. It's the ability to have a continuing business operation that is funded by stockholders and to keep those stockholders happy.

So given that that's a big issue here and a real concern, what I would challenge this conference to think about in the broad context, and I'd love to hear what the panel thinks about it, is, what's the alternative? How are we going to develop medicines to treat unmet medical needs? How are we going to have safe reliable diagnostics? And I take a little bit of issue with Dr. King. You're not done when you find the mutation. You really have to have a regulated industry there as well because there are tragic outcomes from poorly done commercial diagnostics. Patients get bad information and make the wrong decisions. You've got to have regulation of that industry as well as the pharmaceutical industry.

What's the alternative model to the one that we have now and does intellectual property have a role to play there? Right now it's critical to the profitability of the profit-driven industries that are the bulk of new drug development, and let's face it, new diagnostics. Thank you.

AUDIENCE MEMBER: What's the alternative? How do we do that otherwise?

PROFESSOR KUSZLER: Professor Huntsman?

PROFESSOR HUNTSMAN: First of all, thank you very much. I would like to encourage not only the speakers and panel now but throughout this conference to, when possible and appropriate, also speculate a little bit about the possible impact of some of the big changes

underway in science and health and their future impact on our ability to actually successfully develop new devices and drugs in a commercial setting.

For example, the shift toward a value orientation in healthcare. What's a likely impact of that? What is the likely impact of the enormous progress in precision medicine and our ability to maybe narrow patient populations? What's the chance that the word "indication" is going to become a quaint artifact of legal history? But for right now, I'd like to ask you about the perception that there is an increasing debate underway. I know that there are veterans of drug development both in pharma and in the biotech who say that absolutely you need protection. You need intellectual property protection in order to pursue these therapies, but that patents are really not a very significant part of that protection.

They say that -- they argue that when you look historically at the actual marketplace of drugs, that patents have been relatively insignificant except for the comfort they bring to investors. What's your perception about the actual importance of patents in the constellation of intellectual property protection that firms need to do this work?

DR. THOMAIER: I can give you a very short answer, maybe my colleagues may have different ones. I'm completely convinced that it's an extremely important part to drive innovation and not only to have the business but to drive the innovation in these parts. That's my conviction. That's what I see in research in drugs in the past. If I wouldn't convince personally, and this is not really personally, personally that this is the case, I wouldn't work in the area. But my personal opinion is you're wrong, it's not a small contribution. It's pretty important. And I have not seen yet any -- and that's I think the one topic of this conference, right, not seen any real idea where I would buy in and say that could be an alternative to safeguard of health research. That's my personal view and that's not even Bayer, that's me, yeah.

PROFESSOR KUSZLER: Yes, Professor Russell.

PROFESSOR RUSSELL: I brought up that issue of open domain research as being perhaps an efficient way to research and get beyond the initial steps. My colleagues like Chas Bountra, when they do a public talk, and it's a great shame he's not here to evangelize to you all, he will show pictures of how dominant the crowd effect within the companies is. They all work on the same targets, often in very parallel ways, even if they turn out to be nothing. There's a pain pathway called TRPV and he has a slide showing that 12 companies have done this all in secret in competition and nothing's come out of it. Another one that he illustrates nicely is looking under the streetlight, you know, if you're in the middle of a busy street and you only see what's beneath the streetlight, you aren't actually getting the big picture.

And kinases are an extremely important potential target in all sorts of therapeutic areas, particularly cancer, and until a few years ago, there were probably only a dozen or so which pharma companies would work on. There are now known to be something, if I've got the figure right, in excess of 300 in the kinase family.

So what the structural genomics guys do is to produce crystal structures and proteins and things, all these other things that may be involved in biological processes, each of which could have some specificity if you've developed the right small molecule. And I think the inefficiency of the industry maybe points to the need to do some of the early stage identification of targets in the public sector in an open way and then go on from something that is handed on to them from government, finance or charity-financed research, often in partnership with industry who will fund this thing collectively rather than just individually.

PROFESSOR KUSZLER: I think that's a good place to stop. We've had a very robust discussion and I think we've seen the diversity of viewpoints on innovation, patenting, and bringing

it to the marketplace and to help and improve public health. So let us disband for a brief break and thank our speakers and our panel for this wonderful start to our conference.

[Applause.]

PANEL I:
DRUG DEVELOPMENT AND APPROVAL PROCESS WITH ITS PART IN EXCLUSIVITY

Moderator:

Jin Ooi, *Allen & Overy (London, UK)*.

Panelists:

Dr. Peter Feldschrieber, *4 New Square (London, UK)*.

Stefano Marino, *European Medicines Agency (London, UK)*.

Hiroko Inazumi, *Japanese Ministry of Health Labor & Welfare (Tokyo, Japan)*.

PROFESSOR TAKENAKA: Please have a seat so we can start.

MR. OOI: Good morning, ladies and gentlemen. We're on to the first panel session today, drug development and approval process with its part in exclusivity. My name is Jin Ooi from Allen & Overy in London and I have the honor to moderate a very distinguished panel of experts who will help illuminate our thinking and hopefully provide fodder for what I'm hoping to be some lively debate after each of their presentations.

So just introducing them, the first speaker is Dr. Peter Feldschrieber who's a physician and also a barrister in London. He specializes in healthcare and medical law including healthcare products liability, pharmaceutical and medical devices regulatory law, clinical negligence, personal injury and medically related employment litigation. And he's also the editor of a book entitled *The Law and Regulation of Medicines*, which I have to admit to having consulted before preparing for this session.

To his right is Mr. Stefano Marino, who is the head of legal department at the European Medicines Agency. After a short stint practising in private practice, he moved on to the in-house legal sector where he has held a career in the pharmaceutical industry working as general counsel for the Italian groups, Menarini and Sigma-Tau. He also has experience as an intellectual property contracts manager in a global petrochemical company.

And to his right is Ms. Hiroko Inazumi who is a government official with the Ministry of Health and Labor in Japan. She works on policy and drafting laws and regulations and has also been primarily involved with health, including making policies for drug approval and ensuring a stable supply of blood products and vaccines. Unfortunately Dr. Mustafa Ünlü can't be with us today due to unforeseen circumstances.

Just a quick slide of what is the long road to a new medicine and I think we've touched on this in this morning's panel already. Three words come to mind: One, being expensive; second, time-consuming; and thirdly, uncertain. So I guess with that in mind, there is a quid pro quo for pharmaceutical companies to be given an opportunity and the incentive to recoup the considerable investment in the drug development and approval process. And one example that comes to mind is BMS's drug taxol which didn't have any patents on its active ingredients. Had it been approved immediately for generic companies, BMS would not obviously have had any incentive to incur the extensive costs to develop, test and bring taxol to market.

So the fact that both patent protection and data exclusivity provides incentives reflects the dual nature of the drug development process. We all know that exclusivity drives the pharmaceutical industry. On the one hand you've got the innovators as I said spending considerable

amount of money and resources in bringing drugs to the market. And at the same time on the other hand you've got generic companies who are also looking to bring their generic drugs to the market.

And patenting here being one of the main routes to exclusivity. But in the situation of BMS, for example, patents may not always be available or some will say it doesn't give sufficient time for companies to recoup a reasonable return of significant investments made. So there are additional exclusivity strategies involved and I think we'll be discussing some of this today. And this is just a table showing a quick comparison between the regimes in Europe, the U.S. and Japan. And again, one underlying feature that I have in mind is the tension between public health objectives and the commercial incentives for innovation. Is the current system a balanced one or if the scales are to tip one way or the other, which way should it tip?

So with that in mind can I please introduce the first speaker, Mr. Stefano Marino.

[Applause.]

MR. MARINO: Thanks very much. Thank you very much to the University of Washington and also to UC Yale for having invited the EMA and myself.

As you know, the EMA, the European Medicines Agency does not deal with intellectual property. However, I have dealt with intellectual property practically all my life. So when Sir Robin called me to ask me whether I was interested to come here, first I thought he had the wrong telephone number, but I was so driven by his speech on the phone, and I know that for most of you, for most of us, he's been a living legend for all IP scholars. He's still a living legend and I literally could not refuse, so that's why I'm here.

Well, the deal was that I would not present, I would not give you any presentation today. I prepared my slides because I'm normally a medium diligent guy but I said, well, we're going to use them with the agreement of our moderator only for the "questions and answers" slot. And then I was made aware last night at dinnertime that the FDA representative could not make it, I was asked to replace him. So, instead of giving you one presentation, I'll give you two today. Not the FDA-related one but both dealing with European matters.

Anyway, time is running and I'm very much afraid of the sanctions that I could incur. So, my first consideration today in this very interesting conference, and also listening to the first panel of the morning, I just was asking, talking to myself whether we have an IP issue a regulatory issue, an economic issue, pricing and reimbursement-related, or we have the three of them altogether and what is the role of the regulatory agencies in this complex world today. For example, the concept of a medical need, which from we understand from Inazumi's presentation is at the heart of the debate that normally investors undertake, is one of the concepts that is most debated currently in Europe. What is a medical need? We thought we knew it, but the more the science goes ahead, the more the medical science goes ahead, we have to ask ourselves whether our regulatory interpretation does fit with the new awareness about this concept.

And just to give you a very quick snapshot, is a medical need met or unmet only when there is a major therapeutic advantage of a second drug over the first one, or shall we instead reason in terms of what is satisfactory from a medical viewpoint, from a scientific viewpoint?

Well, these are the current questions that are giving us some headaches, in particular, as I will show quickly later, when dealing with new attempts that in Europe we are trying to make in order to attract more and more investments in R&D in our continent, like the adaptive pathway scheme or like the priority medicine schemes. So what I will do now is to give you a very quick picture of what is in Europe the current landscape. I don't need to annoy you with what is the scheme of data protection or market exclusivity. You're all familiar with those concepts that are in our DNA since many years; so presumably we are all talking the same language here.

But in Europe, we have quite a generous, I have to say, system of rewarding pharmaceutical research and development efforts. And as you know, in 2004, the Union has chosen this "8+2+1" system which is so far still the best in the world, at least on paper. It remains to be seen whether the case law of the European Court of Justice or the interpretation given by the European Commission and the practice at the EMA are consistent with what the legislator wanted to achieve, but so far, if you see the slides comparing our rules with the U.S. rules, the Japanese rules and others, I'm not joking when I say that in Europe we have the best system for rewarding R&D efforts in pharmaceuticals.

So as you know, there is a general harmonized protection of eight plus two years, and if a second indication of an authorized product is approved within the first eight years, then you also may enjoy an additional year of data exclusivity which in fact protects your product for a total of 11 years. And so the return on the investment for those who invest in Europe and actually launch a product in Europe is not bad. And hearing also the presentation given this morning, if I were that investor, I would probably believe that Europe is a nice country to put my money into. It depends then, as I said, whether particularly at the price reimbursement level of the national Member States, there is the same attitude to reward innovation or not.

In the particular field of orphan drugs, there is an additional protection or an additional award because a second orphan product cannot be even submitted to the European Medicine Agency for evaluation, unless it shows a significant clinical superiority over the first authorized. So the legislature wanted to give an additional protection to the orphan drugs which are neglected. These are neglected products, and even in that field, as you know, the European legislation is very generous compared to others, including the United States.

So, very quickly, this was the previous system before November 2005 and after November 2005 and you will find in this slide, I don't need to annoy you again, all the details concerning the Member States who previously had a six-year protection. This is a summary of what I just said before, but if you see the little arrow, orange arrow at the right-hand side, you will find that, unfortunately, there is only an extra year of exclusivity for the new indication. I say unfortunately because in my industry days I was advocating and I was fighting hard in order to get additional protection for new therapeutic uses of existing drugs, but then at the time, the EFPIA had to make a choice between various options and they believed that if we had insisted for an additional protection for the subject matter of this conference, we would have probably had a clash with the EU Commission for the "8+2+1" 10 system. So a political choice was made. It's not up to me to say today whether that was a right one or not, but I'm very glad to hear that there are many in this room who believe that at least now there is a need for an additional reflection on these issues.

And in fact, the new indications, where there has been significant pre-clinical or clinical studies, get only an additional year of data exclusivity.

So this is the system at the moment. Again, I will go quick, otherwise I will exhaust my time and I will not have time to brief you on what we are doing in Europe at the moment to foster innovation, but this is the summary of the existing protection rules. And when it comes to the orphan medicine or products, as I said before, as you can see here, the situation is even more generous. In two recent judgments of the European Court of Justice, it has been more or less clearly stated that the orphan field is quite a special one and probably is the one that deserves additional consideration and additional protection by the legislature.

One of the cases is under appeal at the moment so I will not comment on that, but in the words of the Court, certainly there is room for a special protection of the orphan drugs. And coming back to what I said before, considering the unmet medical need or the concepts of significant

benefit or a major therapeutic advantage over existing therapies, perhaps there may be the room to distinguish between ordinary drugs and orphan drugs.

This is a long road. We are still discussing at the moment with industry but also with the Commission, and there is a guideline on orphan products which is underway. It's going to be produced soon by the Commission in 2016, but this is one of the areas where perhaps a distinction between the same concept of significant benefit in one area and the other area may find some room. Again, here is just to say that the orphan medicinal products, when combined with paediatric investigation plan, when the PIP is completed, they can get additional two years. So this is another signal of how, in 2004, the legislature wanted to give additional boost to the development of these orphan medicinal products.

And this again will be a sort of summary line, executive summary of that protection. The last two slides -- before going to the future plans, concern a recent judgment given on the 15th of September, 2015 where the Court upheld the Commission's interpretation that the periods of data exclusivity are counted from the notification date of the decision, i.e. not from the date of adoption, but from the date of notification to the company.

So this is important because sometimes even a few days may change significantly the economic impact both for the generic manufacturers who want to go to the market and for the originators who want to remain in their monopolistic situation. The Court has clarified that the correct date to be taken into account is the date of notification. This slide is about the famous rule that gives companies a lot of headaches, the Global Marketing Authorization. This was enacted in the legislation after a couple of important judgments by the Court of Justice in the '90s. All additional strengths, pharmaceutical forms, administration routes, presentations, line extensions in a nutshell, they are part of the same global marketing authorization. As such, they cannot get additional periods of protection.

All these authorizations belong to the same one, therefore the "8+2+1" applies only once. And again, there has been a very recent judgment by the Court, who has clarified in the Novartis case of 15th September 2015, that even when the marketing authorization holder has received a second marketing authorization, and even when a new name has been used, if the active ingredient is the same, they belong to the same global marketing authorization, so only one period of data exclusivity applies.

Is that sufficient? Is this a very nice construction or is it just the most generous scenario on paper only?

If you think about the impact that these judgments by the Court have had on the long-term marketing plans, you may understand that maybe this scenario is not exactly the best that one could think of, in a continent where the R&D efforts, in particular the clinical trials, have been declining sharply in the last 10, 15 years.

What is EMA doing at the moment? We have launched recently two programs, we call them pilot plans. The first one is called the adaptive pathways, it's a very popular concept in the United States so I don't think I need to spend many words, and it was very successful. And the concept of adaptive pathways is very much focused on the wise use of an instrument that has not been used very often in Europe, which is the conditional maximum authorization. I don't need to spend too much time on this and we can expand later on if you wish.

In addition to the adaptive pathways, we recently launched, and it's open to public consultation now, what we call the "PRIME-priority medicine" system which is essentially, as I call it, a business class scientific advice given to companies at the very early stage, even in the design phase of a new product. The EMA is offering companies to assist them with the design of

these new products so that they can go to a very targeted program of preclinical and clinical trials, hoping that, by doing so, the result at the end will be satisfactory.

We decided to do so not only because there is a very successful system in the United States, the FDA breakthrough designation, but also because we believe that if we don't do so, Europe will probably meet a new phase of decline in terms of investments landing on our continent. So what is PRIME? PRIME is the possibility to enter into this business class scientific advice scheme very early, by proof of concept, so prior to Phase III, based on very few clinical data, but significantly showing that this product has a therapeutic advantage over existing therapies. And even at the early stage of proof of principle, prior to Phase II, by exploratory clinical studies, particularly when small enterprises or even academia are involved.

So the main organizational innovation here is that a rapporteur, CHMP rapporteur will be appointed earlier. Today a rapporteur is appointed much later, of course. But this will guarantee that there will be very wise and competent guidance from the best experts that the Member States will make available to the European Medicines Agency, so that the company may get the best possible advice.

And then there may be (we are discussing at the moment with the Commission and we are still waiting for the results of the public consultation) incentives for small to medium enterprises and perhaps even for other categories of applicants.

Very shortly there will be an early confirmation of the potential for the accelerated assessment, a written confirmation of the viability for the scheme, an early rapporteur appointment and the continuous presence of the best experts side by side. I mean, they will go hand in hand with the company, and even the financial side will be important because sometimes even the fee incentives may be hard to combine with these new ideas. These slides have been presented by my colleague, Sabine Haubenreisser, who works at the FDA at the EMA liaison office, at the RAPS regulatory convergence conference in Baltimore one month and a half ago. I encourage you to take a look at them in the interest of time and also to take a look at other presentations that were given in that conference where we tried to describe this new PRIME scheme the best we could.

We are very much interested in seeing what will come out of the public consultation and I'm sure that once this will be launched, this may really be a new driver for innovation and for the access of good ideas to the pharmaceutical world in Europe.

I think that before Sir Robin or the moderator jumps on me, I should stop here and I would encourage you to ask questions or even to simply take a closer look at these slides. You will find my address wherever in the presentation. You may even come back to the EMA with written questions, we'll try to answer them the best we can. Thank you very much.

[Applause.]

MR. OOI: Thank you, Mr. Marino. We'll hold off on questions to the end. Dr. Feldschrieber.

DR. FELDSCHRIEBER: Thank you very much, Jin. Well, thank you very much for inviting me to this marvelous meeting, particularly to Robin.

When Robin first told me about this meeting, I said, Why me? I'm not an intellectual property lawyer. I know from nothing about intellectual property law and Robin knows this, and even today I would still be terrified of appearing before you, either a first instance or in the Court of Appeals or indeed in arbitration or in consultancy. So as long as you understand that, I'm on a reasonable wicket. However, he did ask me to be both a heretic and to talk really against what seems to be the prevailing ideology, and what I'm going to say now will probably leave you with wanting to burn me at the stake after I finish this presentation, but I want to go to what I think is

the heart of the matter. I'm a bit eccentric, I'm both a physician and a barrister, and for this talk I'm talking in my capacity as a physician scientist who is affected by the legal framework that I do know a little about.

So what are the incentives for innovation? Well, regulation has metamorphosed in regards to its -- in its regard to its public health objectives since the introduction of thalidomide. And to set the scene, I think that this was a very prescient moment: When thalidomide came on to the market in Europe and Australia, it was done on the basis of having been assessed on limited data. There had been a limited scientific approach even in those days. And the United States was saved from this terrible epidemic of fetal malformations by one woman, by Frances Kelsey in the FDA who refused to authorize thalidomide on the basis that she had not been provided with sufficient data to understand its primary pharmacology. In particular, she asked questions about its potential safety and efficacy.

Now, this of course was in the 1950s, very, very early on before pharmacology some people say became the sophisticated science it is today. But even at that stage it was well known that the pharmacological and pharmacokinetic parameters of drugs needed to be assessed very carefully in order to make an evaluation of benefit risk. This was not done in the submission for thalidomide. Frances Kelsey thankfully refused it and the United States did not suffer this epidemic. However, Europe and Australia did, precisely because there was limited aspect -- limited access to scientific data. And this is the theme of what I'm going to talk about throughout because I think that every major drug disaster and every potential flawed regulatory system has been affected by this particular philosophy which has damaged the use of good scientific practice.

So what are the current objectives of regulation? Particularly they're written into statute in Europe. The European Medicine Directive has explicitly two particular objectives. One is the public health objective as regards to safety and efficacy of new drugs, and the other is to facilitate to support free trade and commercialization of new drugs; in other words, the incentives to develop.

Are these objectives compatible? Well, I don't think so. Public health, the public health objective is primarily towards the identification and the evaluation of benefit risk and appropriate benefit risk for the population at large. That has an ethical consequence, it has a moral consequence to it. Because what we do as regulatory scientists and scientists in development of drugs affects massive populations so we've got to be extremely careful. We can cause drug disasters on the scales unheard of in previous times.

Commercial incentives all -- as far as I can see, all the commercial incentives that have been put together by the regulatory authorities in Europe have depended on data -- on granting data exclusivity and restrictive access to related data in order to allow for what are effectively quasi monopolies and this is against the practice of good science. So these two objectives are potentially dangerous. They're both inconsistent, and I'll give you some examples of how this restricted access to good science has ended up in drug disasters.

So the current commercial incentives, as Mr. Stefano has adequately described, are orphan designation, protection against generic entry by extending market exclusivity, supplementary patent certificates -- and I won't say much more about them. That's an area that Robin knows I know very little about -- and early access schemes. And one other aspect I want to talk about which is reflection of the regular -- of the mood in Europe to ease the regulatory burden is the access to innovative medical treatment which is proposed UK legislation, and I'll talk about that in a minute.

Now, it's realistic, obviously, that if private companies are expected to spend huge amounts of money in investing in research and development, there must be some reward. There must be

some incentive for them to do that. The question is, how much is that incentive and how do you measure that incentive? So that balance has to be struck. And we don't yet know what the potential balancing mechanism should be but I'm going to suggest one that needs further thought in a second.

So it's realistic to incorporate facilitating return on investment to regulation and -- but, and this is the big "but," the incentives should allow proportionate reward. They shouldn't play to the senior management of a company who can say that they have a fiduciary responsibility to their shareholders to maximize profits. That's the current law and that is why companies behave as they do. What worries me is that the law explicitly invites them to maximize their profits, and because of that, you get egregious examples of manipulation.

The recent example in the United States of Turing Pharmaceuticals in taking Daraprim, an old antimalarial drug and raising its price 5,000 percent on the basis of new indications of the drug. That's egregious. That's wrong. That's morally wrong. It's ethically wrong. But that's the kind of opening that these incentives can lead to by being melanistic and bad -- they're bad incentives.

We see similar things like this with some of the examples I talked about just now. Orphan designations for rare diseases. This provides a quasi-monopoly, for instance, two years extra market exclusivity for those orphan diseases with agreed pediatric investigation plan. That again, it relies on the inaccessibility of data from product -- from previous products that could be a bridge to justify the benefit risks of upcoming products. It's open to abuse, and I as a regulator -- and I do say I stopped being a regulator some five or six years ago, but unfortunately once a regulator, you're always a regulator. That's open to abuse and I personally experienced some of the abuses.

For instance, malaria, a worldwide scourge has been regarded as an orphan disease in Europe because there are less than one in 5,000 cases of it. Crazy. I had to deny, decline authorization of a drug for Addison's disease. Still, dexamethasone, common drug for steroid replacement in Addison's disease on the grounds that Addison's disease was effectively, epidemiologically speaking, a rare disease in Europe. So here we were, the regulator was forced to deny access to the market of a cheap version of a steroid which was simply performing its fundamental pharmacology collection. Madness.

So all of these schemes have a flaw. They have unintended consequences. Let me give you one example of another drug disaster which is -- pointedly exhibits why this is so potentially dangerous. There was a drug disaster in the United Kingdom a few years ago called TGN1412. This was a cytokine modulator drug that was produced by a company, TeGenero in Germany, with the potential indications of leukemia and autoimmune diseases. That drug was prematurely put into a Phase I clinical trial in human volunteers and nearly all of -- well, okay. It was given -- active drug was given to six volunteers -- sorry. Can I take my glass of water?

It was given to six volunteers and one was given a placebo. All six volunteers nearly died because of vascular complications. At the end of the day there was a major regulator report drafted by Gordon Duff who was chairman of the Commission of Safety in Medicines at the time, Commission of Human Medicines, and he came to the conclusion that the pharmacology had not be accurately defined. The dose response hadn't been adequately defined. They used the wrong preclinical toxicological calculations to extrapolate to a dosing, and those consequently, nearly all six patients died.

However, what -- and he did mention it in the report, but no, there was no authority. There were rumors. There were anecdotal rumors that a similar drug had been tried, had been developed by a small biotech company in Southampton some 12 years prior to the TeGenero disaster and that company had showed in limited clinical studies that cytokine storm was a probable factor, a probable side effect.

Now, had that information been available to the developers of TGN1412, the drug would never have been developed. I can't be the authority for that. I can't give quote -- apart from the anecdotal quote as to what happened and that shows pointedly that restriction of access to data is potentially so dangerous to drug development.

What about the early access to medicine schemes? Well, here you've got a scheme which, quite rightly, is trying to lift the regulatory burden to allow for what we call inverted commerce, a premature access to the drug on the basis of limited data to make a benefit risk evaluation. But if you do that in the -- in the context of rules which disallow full and free and transparent access to the data, how can you make that premature calculation safely? And that in terms has legal consequences. It has consequences in product liability over in Europe, and I know that Robin doesn't agree with this, I think it has consequences in IP law as well because it makes it more difficult to deduce the evidence. I know there are issues of discovery that could overcome this, but nevertheless, the fact that published data doesn't exist even, and it seems simply to rely on data that is anecdotally reported that may have been a signal of potential danger is in itself dangerous.

The orphan designation I've already talked about. The access teams I've just talked about. But do these schemes satisfy the public health objectives in unmet medical need? I think the limited transparency in disseminating information puts a damper on those schemes and that needs to be addressed.

What about adaptive licensing? This is a very, very interesting scientific development. It allows for, on a case-by-case on a therapeutic-area-by-therapeutic-area basis to design clinical studies that will be practical, pragmatic and effective in giving sufficient data to assess benefit risk. It's predominantly being looked at in terms of biological molecules. These are molecules with potent pharmacology. There is limited safety and efficacy data on it, and new modes of action in particular may not be fully understood. So they need as much data as possible to make as robust as possible a risk benefit analysis. And yet, that robust data is deliberately not being made available.

Maybe I'm overemphasizing my point but you get the gist of it. The legal issues I talked about. The product liability and negligence, I think this is very important one. It hasn't raised its head in Europe in litigation yet. I suspect it may do in the United States. There have been several issues with drugs that have failed on the basis of inadequate data. The most startling of these of course was Vioxx. Vioxx was withdrawn as an anti-rheumatic by the company on the basis of challenges by the Security Exchange Commission in New York, but nevertheless, it had to be withdrawn because there was data within the Vioxx -- clinical data support further that had been submitted that failed to be transmitted to the population at large, that the drug could and did cause morbidity and cardiac mortality. On a very small scale, but nevertheless, the drug failed.

And here we have an example, paradoxical example of what is a marvelous drug which was a major scientific benefit had to be withdrawn because of the inaccessible and lack of transmission of data on safety and efficacy to the population in large. Again, that's a paradoxical, unintended consequence of the regulatory framework.

So what are my conclusions? Well, there's a common theme that I've tried to describe here. First, comprehensive a database as practically possible in all drug developments. I think that at the moment all incentive schemes, or at least those have been drawn up in Europe, seem to hinder this, and we need a rebalancing exercise. I'm not denying the fact that there has to be a reward system but what can that reward system be? My own view, and I haven't thought this through fully and I would very much welcome discussion on it and I'd very much welcome if possible some kind of working group to really flesh this out.

It could be that the metric, that the fulcrum of the balancing exercise could be the health and technology assessment and process, the kind of process that's developed by NICE, National Institute for Health and Care Excellence in the UK and Health Technology Association databases, assessment databases that have been generated in the United States. This could provide a metric - as the database builds up, this could provide a metric which could itself be a benchmark for both the regulators and the companies and governments when they go and talk about reimbursement in pricing, to suggest quantitatively what is a recent and proportionate return on investment in particular therapeutic areas? I understand that you can't do it for every medicine particularly as we're moving into an arena of personalized medicines, but there should be some framework where we can have a generalized view of what health technology assessment thinks the benchmark should be.

On that, I leave you a very open question. I hope you're not going to burn me at the stake. I have some friends here who have in the past instructed me, I know they won't instruct me again, but never mind, maybe if I stick to intellectual property law I'll be in better shape. But thank you very much.

[Applause.]

MR. OOI: Thank you for a very thought provoking presentation. Ms. Inazumi.

[Hiroko Inazumi speaks but is not written or transcribed.]

[Applause.]

MR. OOI: Thank you, Ms. Inazumi. I guess before I open the floor to questions, I was wondering if the panelists have anything to comment on your other panelists' topics? No? I'll just open the floor to questions then. Yes, please.

DR. DRESSEL: Jurgen Dressel from Novartis. My question is to Mr. Stefano Marino regarding centers for new indications. You mentioned in your presentation we have the eight plus two plus one scheme, which in Europe of course runs at the same time as usually compound patent production or other protection is running and I would say, at least according in most of the cases, expires earlier than the compound patent protection, especially including the supplementary protection certificate. I do appreciate the issues with the global marketing authorization concepts and the reason about this decision, but could you imagine that there could be a separate kind of data exclusivity for new indication similar let's say to the Japan or U.S. in Europe?

MR. MARINO: Well, I could imagine it. No, in fact, by reading Inazumi's slides on the additional protection that there is in Japan for those new indications, I only regret that in 2004 the EU legislature did not think with a sort of far-sighted approach, because more medium enterprises as well as generic manufacturers, I think they would have incentivized to explore these new avenues. I can only -- as you very well said, I can only imagine that the situation could change. At the moment, as you know, to change the legislation is a pretty much laborious mechanism in the European Union, but let's not lose our hope for the future.

MR. OOI: Yes, please.

PROFESSOR TOUMI: I have two questions about Japan. One of the questions is about orphan drugs. How do you explain that the orphan drug regulation has been so little successful? There is about 300 products that have been designated as orphan drug in Japan compared to few thousand in Europe and the U.S. And the second question is about the introduction of an HTA assessment in Japan where health economics is going to be part of the assessment of the new drugs. Last week [a company] has issued guidelines on how to perform health economics for drugs and they announce that it could be in force in April next year.

How does this impact the incentive for development in Japan for new drugs that you have presented?

MR. OOI: Can you give your name and affiliation, please?

PROFESSOR TOUMI: Sorry. My name is Mondher Toumi and I'm an affiliated professor of public health at the University of Marseille in France. Thank you.

MS. INAZUMI: Very difficult question to answer. I know the first one is, I think when initiative MLW decides to designate orphan drugs, if there is high predictability to accept, to develop successfully, we designate as orphan drug. So criteria, I think the criteria to orphan drug designation is a little higher than other countries such as U.S. and European countries. So that's the reason why our orphan drug designation -- the number of our orphan drug designation is limited.

And the next one; I'm sorry. I'm not an expert of the health economics you mentioned so please send an e-mail to me so I will ask my colleagues and answer you later. I'm sorry.

PROFESSOR TOUMI: Thank you.

MR. MARINO: If I may make comments, not on the Japanese situation but in general. I think I would support what Peter was saying before concerning the health technology assessment. This is a very powerful instrument in order to evaluate the real add-on that a new drug may be bringing to patients. In Europe, the Commission launched some years ago and has recently refinanced for the next five years this initiative called EUnetHTA, which is the EU Network of Health Technology Assessment bodies, and EMA is an observer there, but we are trying to make the point that if there's a forum-- well, "centralized" is not the right word, but if there's a hub where the health technology assessment bodies of Europe can gather together with the experts sitting in the Committees of the EMA, and they together take a look at the value, comparative value of a new drug, I think at the end of the day their results may be satisfactory for all, including the payers.

When I say "all," I include industry, the applicant, because of course the process of bringing the product to the market for reimbursement later is painful, is long, but if they can rely on a joint centralized European assessment, that of course would be enormously positive for them as well. And the patients would benefit because at the end of the day regulators have the patients at the heart of their job of their work. And if a patient can get access to this drug earlier, I think the whole community, the whole scientific community would benefit as well.

So I do believe and I do hope that the HTA assessment could be a real driver of innovation in Europe, at least one of those drivers and I do hope that some Member States who are not convinced yet will renounce a little bit to their traditional thinking that because the competence lies with each of them at national level, there cannot be a joint discussion. I think if there is a joint discussion at the end of the day, the evaluation is far better.

MR. OOI: The gentleman there.

MR. OKUMURA: Thank you. I'm Yoichi Okumura of the Takeda Pharmaceutical Company from Japan. Let me somehow make a comment to the questions previously asked about the Japanese processes. The -- I'm very much sorry, I can't tell you the exact process of the PMDA about HTA consideration, but what I know is the PMDA is now deeply considering with the HTA for evaluating a drug value. That's why, for example, the example Inazumi-san showed the Sakigake project, that's the forerunner project, that is I think one of the program run by the PMDA somehow related to the HTA. And of course private sector in Japan are also pretty much encouraged to develop the innovative track. This is the current situation in Japan. And also the question -- what is that?

MS. INAZUMI: Orphan drug.

MR. OKUMURA: Actually many orphan drugs in Japan have been now approved. Maybe a couple of years ago, the private sector initiated together with the government to set some sort of the development system on Drugs for the disease difficult to be cured and also the rare diseases. We have funded to it together with the government. And then it encourages private companies of the pharmaceutical industry to discuss this opportunity and then to deliver those drugs to patients. That's the current situation what I know. Thank you.

MR. OOI: Thank you. Dr. Gonen, yes.

DR. GONEN: Hi, I'm Galit Gonen from Teva. So just to recap from the morning. We talked about incentives for doing researching for new users in established drugs and we started with patents. So Professor Russell's presentation basically demonstrated how problematic this is in view of the requirements, we're talking about established molecules. Then we move on to regulatory data protection which seems more appropriate because we can -- that's the natural vehicle to protect data. There is new research, new clinical data accumulated. We can play with the scope and make it in line with the scope with innovation. Stefano says he could imagine it in Europe as well. It all seems great. But I think when we talk about the incentive, so we talked about patents, regulatory data protection. At the end of the day we need to think about the payers and we need to move on to this discussion, because even if someone has a regulatory data protection and even a patent, why would a payer pay a premium price on a molecule which he has available for other indication.

And I think that's the main -- that's the gist of it and that's the discussion which needs to take place between the industry and the payers, so if the industry as a whole support in this type of research, it brings -- it's good for patients. It's good for everybody. Then there needs to be a discussion between the industry and to payers about premium pricing which will be for the value. And I think linking to the presentation from Japan, which I found was fascinating, it's the first time I've ran into a price which is set on the basis of R&D considerations rather than only on the basis of value considerations. So if you can elaborate more on this point of your presentation, how it is done, how the R&D consideration is taken into account in discussion between the payers and the industry.

MS. INAZUMI: I think the incentives I explained is firstly the industry started to offer these incentives to ministry so -- oh, I'm sorry. I can't speak very well. Do you have any ideas to explain at all?

MR. OKUMURA: Yoichi Okumura again. Honestly speaking, I don't know exact deeper process about pricing., Usually so-called NHI drug price is an official drug price given by the government. To obtain it, the company provides relevant information, including sometimes expense for the development of the drugs and also cost of goods of the drug and also some sort of a reference price of competitive products on the market. Those things are entirely managed by the government. That is what I can tell you today.

MR. OOI: Thank you. Now, discussion on pay is actually very interesting. I wonder if Mr. Marino and Dr. Feldschrieber have any comments on that?

MR. MARINO: I have some comments but --

DR. FELDSCHRIEBER: No, no, you go first.

MR. MARINO: No, I agree with Galit. The payer is the real problem, the real hardship, especially when you have an economic crisis that really strangles every attempt to do better. One thing that I have to say: historically, the evaluation of R&D efforts made by companies, like one of the tools to give a better price, a premium price for a drug, has also unfortunately led to undesirable results. There have been cases in the late '80s and early '90s where in some countries

of Europe at least, this has led to major deviations from the good tracks, and you may recall some egregious cases of corruption and biased evaluation made by payers at the time in various countries. Unfortunately my country was at the forefront of that attempt.

But perhaps the route is to have a very robust health technology assessment, because that would be the basis for the payers at a national level to then decide based on their national legislation. In Europe the competence lies, as I said before, with the Member States. EU does not have a competence in pricing and reimbursement, but based on a very robust health technology assessment, perhaps centralized, or if we don't want to use the word "centralized," at least harmonized among the various bodies, I think that the national payers would have an additional tool based on their own legislation to give this premium price.

And finally, one more thing. You are very right, there is no real hope that new drugs may be brought to the mass market even using these additional schemes that we are trying to promote, like adaptive pathways. And in fact, one of the features of adaptive pathways, the way the EMA sees it, is that the payers must sit down with the companies much before, not only when the drug is ready, the approval is granted by the Commission, and then they start negotiating the price and it takes 18 months or 24 months to get reimbursement.

One of the core issues of adaptive pathways is to launch a sort of early discussion before, so that the payers can see the drug while it's being developed, and particularly in the first 12 months of the conditional marketing organization (which could be 90 percent of the cases. In those 12 months, the payers will have a look at that.

So without new ideas, Europe is a different world with respect to Japan and the U.S. If I may say so, it's a much more difficult world to live in because you have to combine 28 member states experiences, national systems, payment, advertising, it's complicated. But we are trying to do our best in order to harmonize even in that respect.

DR. FELDSCHRIEBER: I agree entirely with Galit, she makes a very valid point in trying to get some harmonized quantitative view of what the payers think and realize would be a benefit with the drug and inject that into an HTA assessment. I think it's terribly important, and despite all the difficulties that Stefano said, I think we should start setting up mechanisms to do that. And it can be done. There are organizations in Europe which would actively cooperate with one another -- with each other. And my suggestion would be that it's not just individual HTA, health technology assessments on particular drugs. In parallel to that, you have to build up a benchmark of comparative HTA assessments, both across therapeutic areas and across geographies. And that can then be interrogated as part of this final decision-making point as to what the return on investment will be.

So you could qualify it for a therapeutic area. You could qualify it for a patient population and qualify it in -- I don't know how to describe this properly, political, patient lobbying terms.

Now, this brings me to another point: We have here an example of big data, very big data, and it's up to the regulators and the pharmaceutical scientists I think to try and devise methods as to how to interrogate this big data because that in itself would add to the tool. I'm talking grandiosely, I realize that, grandiosely and expensively, but I think that we could start with some kind of working party to put these ideas together and then flesh them out in terms of regulatory submission.

I don't think it's going to -- it shouldn't take that long to do this because this is very, very important for patients to have a trust in what they are paying for as taxpayers ultimately, for the innovation of new drugs.

What do you think, Robin?

SIR JACOB: Well, I'll go back a little bit and talk about your talk. The word "patent" means open. The basic idea of a patent system means that information is put out there. The protection given by the regulatory system is closed. It's the opposite of patent. And I think quite a lot of criticism of the pharma industry is indeed that all that data is private, and in principle it's a bad thing, which is what you said.

Similarly, a lot of other data is kept private and I think that's unfortunate too. Some of it is even protected by privacy laws. Now, if I was given charge of things, first of all every prescription would say what the medicine is for. Why? Because later on you're going to want to know whether it's working for that thing, and a much better idea if you can mine the data of all the patient records, which brings you back to the personal thing, of whether it really is working, then you're going to have a much better idea whether it's working for other things because the patient records would happen to contain all the other things and suddenly you'll find correlations which you would never have noticed. And the history of science is about competitive scientists but also open information.

So my own view is, it's a great pity that we have to have regulatory protection but it's a good deal better than having no protection. So if you replace it by an open system for regulation where the regulators are concerned with one thing, does it work and is it safe, and the scientists are creating new uses for old uses or old established medicines and using that data to find more things and learn more things, that would be an ideal system but we've got to put in place some other system to pay for the industry.

And it's no good bemoaning it and saying, Oh, well, there are all these wicked capitalists making money out of this, because the question was asked earlier, you got any better ideas? Jamie Love, "Give him a prize," he says. Well, that's pathetic. They tried prizes in Russia. Prize systems have never worked for innovation except once, longitude, the chronometer. But even then it wasn't a very satisfactory story for those that read that wonderful book called Longitude. But you're not going to have prizes from governments or anybody to pay the \$120 billion a year coming out of Big Pharma, you're just not going to get it.

So those who want to come and say the patent system is no good are talking destruction. Every CEO of a pharma company must wake up in the morning sweating, every product they sell which is making profits now will be out of patent and making hardly any profit in 10 year's time. My company is going bust unless they find something else.

So the focus must be for leaving the system for new medicines, new molecules as it is, and looking at ways to encourage research into other, apparently less profitable things. And it's the same problem which we've got for personalized medicine. If you can't sell the pill at a reasonably high margin to 100 patients of whom it benefits 10, and you're only going to give it to the 10 who you know it's going to benefit because personalized medicine is coming and you can figure out whom it would work on, can you charge 10 times as much? And if you can't, what's going to happen to the research?

The same problem for the cures. I mean, this industry is moving to a bit of a crisis because -- with mass medicines. Now we're going to have cures. Cures are not very profitable to the pharma industry. What are you going to do? We've just learned that there's a cure for most common form of Hepatitis C. It's a couple of injections or something like that. What are you going to charge for it? 70,000 pounds? Actually cheaper than treating the way you treat them now, but it doesn't look like that to politicians.

Now, I think this industry, which has served mankind extremely well in the post war period, is under the very severe threat. There, you've got all my thoughts all packed up in one piece.

As regards openness, I think we should be looking at ways in making it more open and yet providing the protection which the closed system provides now. And viola, that's the question. I think the answer may lie in Galit's question, it's the payers, deep down it's the payers. Governments in some European countries, insurance companies in others, insurance companies in the United States, it's the payers. They should be paying for the research which is going to be done.

MR. OOI: That's a very intriguing idea. I was wondering if there are any views from the U.S. perspective particularly because we don't have a U.S. panelist on board? Or if anyone has any other questions or comments?

MR. FEHLNER: So you'll probably be sick of me pretty soon. Paul Fehlner again from Novartis. So one point of clarification on data. Data protection is in place because the generic companies are allowed to refer to the proprietary data that the originators generated and that reference saves them a boatload of time and money, they don't have to conduct their own clinical studies. This is a benefit for society.

The more robust data protection is, that is, the longer or having a set period of time, and we like Europe, 10 years before that data can be used by others, makes it more possible for us to publish our data. And a concern from the pharmaceutical industry isn't Europe or the United States because there's good robust data protection there as well as patent protection, it's in countries where we can't necessarily rely on the patent system and the data can be used from Day 1. And that kind of short circuiting or free-riding creates a very difficult situation for us at least to invest in launching drugs in those countries.

And let's face it, the innovator is probably in the best position to launch a product, to monitor its safety. We have a real compelling obligation both legally and ethically to do that, and a generic company that's free-riding on our data may be less so. But the question for me is, if we eliminate the leverage that the innovator company has through patents, which has been pointed out, are a mechanism for disclosure, because we don't have patents, what we have are trade secrets and that's keeping things quiet.

If we don't have good data protection, if the company don't have these levers, how do we negotiate with the payers? Because they have the money, and I just always am cognizant of the golden rule, who has the gold makes the rules.

MR. OOI: Any comments on that from our panelists?

DR. FELDSCHRIEBER: From my point I'm not advising resigning from patent protection. I realize it is the one effective mechanism that has to be maintained. What I'm concerned about is the balancing between these two seemingly inconsistent objectives and I need to find a practical mechanism which allows that balancing to take place on a proportionate scale.

MR. FEHLNER: Just to be clear, I think my question is, if the innovator companies don't have the benefits of patents or data protection, how can they counterbalance the interest of the payers to drive prices as low as possible?

MR. OOI: Bryan, perhaps you -- were you going to ask a question or were you going to comment on that?

MR. ZIELINSKI: Well, I did have a question. When you say it should be proportional, do you mean the regulatory exclusivity should somehow vary?

DR. FELDSCHRIEBER: No, no, I don't think it can vary by case to cases. If it's a principle of law, then it has to be harmonized, irrespective of what cases come before the Court. I'm saying that the return on investment, the quantity of reward of patent need to be assessed in a more robust way than it is in the moment, and that's why I'm suggesting HTA databases to be used to that effect so you have a reason.

MR. ZIELINSKI: So it's a price that can be charged then?

DR. FELDSCHRIEBER: Sorry?

MR. ZIELINSKI: It's the price that can be charged for the drug? Is that it?

DR. FELDSCHRIEBER: I have not thought that through. I must admit that. I don't think -- if it's the price that can be charged for the drug, that would depend on market demand, that would depend on political issues, political lobbying by the patients, emotive issues, and that becomes egregious.

MR. ZIELINSKI: I think right now I think Europe has it roughly right --

DR. FELDSCHRIEBER: What's that?

MR. ZIELINSKI: I think that Europe has it roughly right. I think the difficulty is in their uses, particularly new uses at the end of the product life cycle or after it. You can give data exclusivity, but it may not be enforceable data exclusivity because of off label use. So it could be a meaningless gesture. So you have to somehow overcome that.

DR. FELDSCHRIEBER: Overcome that, yeah.

MR. ZIELINSKI: I really appreciate this conversation and I think it points out the fact that the regulatory processes and regulators stand at the nexus of the major problems that confront pharmaceutical development, and clearly, one of those problems is the creation and maintenance of incentives. But the other big one is that drug development costs too much and I'm wondering, particularly in light of Sir Robin's comments, we're in this era of precision medicine and companion diagnostics such that you more and more can't identify that subpopulation of patients who will respond to a drug and that creates great marketing problems. But it also perhaps creates the opportunity to address clinical trials a little differently.

If we look at the cost structure, an overwhelming amount of the cost is in clinical trials, and so you can imagine with precision diagnostics that you can have a much smaller trial size to demonstrate efficacy. But we have this overhanging concern with safety, and so from a regulatory point of view, is there any potential, are there any good ideas out there about how we could evaluate safety with smaller clinical trials and then -- and thus lower our total costs so that we can change the cost side of the equation as well? What is the attitude of regulators toward post market surveillance as an adequate approach and what other ideas do you have?

DR. FELDSCHRIEBER: Can I preempt? And I'll give a lay opinion and then you can give a professional opinion. What you're saying is that you can amplify the power of studies by identifying those subsets of population, and that will make a very dramatic difference in the size and duration of clinical trials to show efficacy, efficacy and effectiveness. What it may not do of course is enhance the power of those studies to exhibit signals of safety. But in parallel with that, the initiatives of what Stefano was talking about, particularly the -- what I'm saying is that this suggestion of defining subsets of populations to go into efficacy clinical trials greatly enhances the statistical power of those studies so that you can get conclusions on efficacy and potentially effectiveness in HTA assessments much, much earlier, but it doesn't allow for an amplification of the power to detect safety seal.

But the regulatory initiatives in Europe at the moment, the early access to medicine schemes, coupled with the identification of innovative medicines, orphan medicines and so forth, personalized medicines, that will allow a faster conditional assessment of what the benefit risk is, together with the resources needed to monitor the patients post marketing and to take effective steps if the benefit risk study -- if the benefit risk evaluation changes. What it does demand, and this is where I leave it to Stefano, is huge investment in post marketing authorization studies.

MR. MARINO: You have a very well taken point, and in fact, one of the features of priority medicines pilot scheme that we are trying to develop now is how to keep the same positive risk benefit ratio and so to not release at all the concept of safety for the patients, allowing at the same time the applicant to come up with lesser, more targeted data, for example for a small subset of population and then have predictions for a positive successful outcome in a broader population.

Now, this was one of the features of an instrument, as I said in my presentation, that has not been used much by companies, which is the conditional marketing authorization, granted for 12 months. This entails assessing the data that come from real life, from market, and see after 12 months whether it should be confirmed or revoked. There are two more elements that since 2012 have been introduced in Europe and these are the so-called PAES and PASS20, that is, post-authorization efficacy studies, post-authorization safety studies. The EMA negotiates with applicants the conduct of these studies which should cast additional light on the real value of the product.

If you combine all this, ideally what we are trying to obtain is a system where companies spend less in clinical trials. Ethics are also satisfied because you don't go without any medical need, any scientific need, you don't go to perform additional clinical trials that would not be absolutely necessary. The safety of the patients is guaranteed as well.

When the pharmacovigilance legislation introducing these two instruments was enacted in 2012, there was a lot of muttering at the level of companies. They said, Well, why do we have to do that? And even now, I mean we struggle sometimes at the EMA with protests coming from companies who don't accept the evaluations by the committees, for example.

Well, we are there to help. We are there to undertake a dialog with companies. If companies understand that these are tools that may help in the development of new drugs, facilitate the understanding of the value of a given drug and perhaps facilitate the job of technology assessment bodies who then have to give an opinion to the payers, if all this circle is not a vicious one but a positive one, then I think that the whole system would benefit.

One last point I need to make based on Sir Robin's words and also about the gentleman who also made very good comments before, about these new uses. And it's the relationship with privacy. Because of the existence of off-label use, because of the existence of very complicated reimbursement schemes, imagine in Germany or in Italy where not only the central government, but also the Lander or the regions in Italy will have on how much they want to reimburse for the drug, how can all this function if there is no robust control on the prescriptions and on the condition for which the drug is given?

We deviated from that old address of checking the prescription. There was a law, maybe the professor from Marseille may remember that, in France, which I think was very good. New uses of existing drugs were reimbursed based on the prescription and on the medical condition that the medical doctor used to indicate on that prescription. So There was a heavy administrative control on those prescriptions. This guaranteed the reward for innovation and neutralized to a large extent the undesirable effects of off-label uses.

Well, that law, I remember, was a model for other countries but then it was aborted in France because of various reasons, privacy considerations, sort of a top-down approach to give preference to generics, and so slowly other countries in Europe followed that. Isn't it time now to go back to that concept, because in the absence of a robust protection like in Japan, what would be the reward for

those who develop new existing -- new therapeutic uses of existing drugs? Nihil, for all the reasons that have been said.

Is that a desirable consequence of the legislation? I think that all these subjects were liquidated at the time in a very quick way, because we had to introduce the “8+2+1” system. I think politicians should take a look back at these issues and see whether there is room now to come back to the past and see if the future was better 30 years ago.

MR. OOI: Thank you. I'd love for this lively exchange to go on but I'm conscious about not wanting to eat into our lunchtime. So with that, will you please join me in thanking our panelists.

[Applause.]

[Lunch recess was taken.]

PANEL II
DEVELOPING NEW MEDICAL TREATMENTS TO IMPROVE GLOBAL HEALTH

Moderator:

Richard Wilder, *Bill & Melinda Gates Foundation (Seattle, WA, USA)*.

Panelists:

Dr. Tadataka Yamada, *Frazier Healthcare Partners, formerly at Takeda Pharmaceutical: Former Global Health Director, Gates Foundation (Seattle, WA, USA)*.

Maja Larson, *Allen Institute for Brain Science (Seattle, WA, USA)*.

Dr. Anthony Blau, *Division of Hematology, University of Washington (Seattle, WA, USA)*.

MR. WILDER: So this is the second time I'm before you here today and hopefully this will be the last, maybe very briefly at the end to give some closing remarks, but what I want to do is to invite the panelists for the first panel here this afternoon which is the second panel for the conference overall to come up now to the podium. So Tachi Yamada and Maja Larson and Anthony Blau, and we'll get started then with Panel No. 2.

So I'm again Richard Wilder, associate general counsel at the foundation, and I am going to be giving a little bit of an overview of what we do in terms of managing our work here in the foundation. I'll be going into a little bit more detail about some of the matters that Trevor touched on in his presentation. And we have a great panel gathered here today that is going to be able to offer us some very interesting insights to the question about developing new medical treatments to improve global health but from different perspectives. Tachi of course, having come from industry, having been the president of the global health program here at the foundation, having then been in industry, I think has a very interesting perspective to offer. Maja Larson, a good personal friend, a good friend to the foundation from the Allen Institute will be able to talk about how they view intellectual property in connection with the work they do. And I think it's especially important to have her participate here because they have a particular focus on open science with respect to the way that they conduct their work.

And then Anthony Blau of course comes to us from the University of Washington, working at departments of medicine and genome sciences and being a very well-known scientist working in the field. And he's representing, as I told him before the session here today, representing all of science and all of scientists the world over.

And so, you know, I just wanted to say a couple things before I get into my presentation itself is that I think, you know, one thread that binds us together in this panel is recognition that science is critical to finding solutions to the problems that confront us all. And I think Trevor did an excellent job in terms of outlining the nature of the public health problems that we're trying to address in the developing world. There's obviously a distance between scientific discovery and then what needs to be done in terms of developing a product, bringing it through clinical trials and into the market, but it all starts with the science.

It was interesting that Robin was raising questions, some fundamental questions really about the intellectual property system and the role that it plays and, you know, whether the approach that we take is different than that that perhaps might be taken by other entities and I'll talk about that a little bit in a minute. But as I was putting together my thoughts for this, I was

thinking not sort of historically of where we are now or where we might be going say in 10 year's time, but looking back to a very early stage in the development of intellectual property and the perspectives that we have from the foundation's perspective or from industry or from government in terms of investments in scientific research. And many of you would remember -- or not remember perhaps, but at least know of the paper that Vannevar Bush did in 1945 that was called Science, The Endless Frontier, and at that stage of course it was just after the end of the Second World War and looking at the investments that the U.S. government had made in scientific research and asking the question as to whether or not that effort has a role to be continued in terms of government investing in fundamental science.

And the answer was that -- the answer was yes, and out of that report came a decision by the government to invest in basic science. It was interesting at the time that that report also specifically called out the role that industry plays in taking that basic science and transforming or converting it into practical applications to provide positive benefits in the world. Also paid close attention to the interests and the needs of the university sector to be involved as well in basic science and basic research.

And so this report led to greater and consistent funding by the U.S. federal government in basic research, you know, but I was thinking that now, here we are 70 years on, even though it did give rise to things like the National Science Foundation, and I think you can trace back the Bayh-Dole Act to the Bush report from 1945, I think it maybe is a time to take a fundamental look at the institutions we have and, you know, ask whether we might want to revisit them.

But again, science is important. It's a starting point for the work that we all do but we also have to focus very much on those incentives that are necessary in order to get not only the basic research to be done but also the translation work to be done by industry and other participants.

What I want to do now is turn to my presentation and kind of take some of these broader themes about funding basic science and moving that basic science through the process of developing drugs and vaccines and bringing them into market, and in our case, doing so in a matter that pays particular attention to those markets that are of interest to us and then I'll hand it over to the other members of the panel. I think Maja has a presentation and the others don't but --

DR. YAMADA: I do.

MR. WILDER: You do have a presentation, okay. A slide presentation?

DR. YAMADA: No.

MR. WILDER: Sorry. That's what I meant actually, a slide presentation. And we'll just go through the presentations, hopefully 10 or 15 minutes each so it will give us time for discussion.

Let me turn to my set of slides and I have several slides that I want to go through them rather quickly. So the investment challenge in terms of the issues that confront us in dealing with issues involving the world is that there's proportionately a very small amount of money that goes into research and development for neglected diseases, the so-called, you know, 10/90 gap between what goes into those issues that are of prevalence in the developing world versus developed world issues. And so the question is: How then do we incentivize and focus and bring more investment into issues that are of interest to us, as Trevor outlined.

The fundamental challenge, I'm going to go through this one very quickly, but what we want to be able to do -- and Trevor alluded to a couple of instances in which we have been successful in doing this, and basically is moving the graph to the left; that is, to find a way that we can take as much of the risk out of investments as possible early on before we start making very large scale investments in things like clinical trials. And so that's a part of the goal that we have here.

Part of that comes out in, you know, work that was highlighted in terms of looking at existing drugs that might be repurposed where some of the risk in drug development and those instances can be reduced especially in the early stages.

You know, just has historically been the case in terms of the different actors or players that are involved in research and development, at the foundation we engage with a large number of actors or players that are involved in basic research as well as translational research in bringing products into the market, including multinational pharmaceutical companies, developing country vaccine manufacturers, biotech and so on. And of course I would add to the list universities and nonprofit institutions around the world as well.

You know, many of the companies that are represented in this room and those of you that are outside counsel working with companies, will probably see your logos up on the screen, so we do work with a large number of entities the world over. And in doing this work, we have a number of investment tools that are available to us. Most of our funding comes through grants. We also are increasingly making use of what Trevor alluded to which are PRIs, Program Related Investments, and in that context we provide loans, guarantees, fund investments and the like.

The one thing that Trevor alluded to that I think is important to keep in mind is the direct equity investments where we do make equity investments in small companies for the most part that we think have promise in terms of a new platform that we may be able to have broad access to for the work that we do, and we structure the arrangements early on to be sure that we focus on our global access requirements and what we want to have in terms of the outcome for the work that those companies are engaged in and I'm going to talk about that specifically in just a second.

What I wanted to do is to put up this chart, and I've got another one actually just following this to indicate that, you know, as we think about these investments and the type of investment vehicles we have, we also map it against the stages of development of a product from early stage discovery through development, clinical trials and into the marketplace. And so what type of investment vehicle we use is likely going to vary depending upon where we are in terms of the stage of development, not only of the technology, but the products that arise from the utilization of that technology.

And as Trevor indicated, our overarching objective is to ensure that what we call our global access objectives are met. It largely has two sections to it. One is that the knowledge and information gained from our project is promptly and broadly disseminated. And Trevor, you know, mentioned our open access policy that dealt specifically to access to publications published in peer-reviewed journals and the data underlying them. So that is a specific embodiment, if you will, of that first prong of the global access objectives.

The second is that the products that arise from our funding are available and accessible at affordable prices in the developing world, so in connection with that -- and really, this is the last slide that I have for my presentation and it's a very busy one so I apologize for that. But as we engage in these activities and we look at the different funding instruments that we have available to us, we look at the stage of the project that we're going to be funding, the nature of the project, you know, whether it's involving a pharmaceutical product or vaccine or a diagnostic, the question, as Trevor indicated, is to whether it has application in the developed world and therefore is of commercial interest or it's exclusively something that would have market potential, if you will, in the developing world where the purchasing power is relatively low.

All of those questions come into play when we're deciding not only what particular, you know, instruments to use but how we're going to manage the intellectual property in connection with those agreements.

And so as your kind of track this process from early stage research all the way to bringing a product into the market, you know, we're likely in our very early stage agreements, going to have a very broad recitation of our global access objectives, much like the text that I've put up on the slide a moment ago. As we move through the process and the chances of success go up, and even further in the process as we've identified a particular product that we can actually say, this is a product, it's going to come into market, we can start talking about costing. We can start making very specific projections as to what the procurement potential is for that product. Then we can get into the stage where we talk about price and volume commitments and other aspects where we're very, very precise about what we want in terms of the price of that product for the given markets that we're targeting.

And so it's -- you know, it's a bit of a multidimensional chess game actually when it comes to putting in place the agreements and managing them and the intellectual property in connection with the projects that we fund. But as I said, it very much is driven by the markets that we intend to serve at the end, where we are in the development stage of a given product, and also this question of whether this product does have commercial market potential, which then goes to the question of exclusivity and how then that exclusivity plays into the incentives of getting the different parties interested and involved in the project from the beginning, as well as interested and involved in making their own contributions to the development of the product.

I didn't actually have anything more for my formal presentation so I'm going to stop here and then hand it over to Tacheta Yamada, but what I was going to suggest is that what we can do is hold off questions until we've all had a chance to give our presentation and then we can have a discussion amongst ourselves, the members of the panel, as well as opening it up to the questions for the group as a whole.

So with that I'll stop and hand it over to Tachi and you're welcome to come down here or you can speak from the --

DR. YAMADA: I'll speak from there.

MR. WILDER: Great. Thank you.

[Applause.]

DR. YAMADA: Thank you, Dick. I used to work here, very happily, and I was a little worried when I understood that Trevor and Dick were going to give presentations that I would actually say the same thing that they were going to say. But I really wanted to focus on what the problem is and how to fix it. So at the Gates Foundation, when I worked here and today still, the biggest problems maybe that they work on are HIV, tuberculosis, malaria. And let's look at those conditions.

HIV we have drugs for but it's been almost 35 years. Next year will be 35 years since the first cases of HIV were reported in MMR Weekly, and we don't have a vaccine. We think a vaccine is easy to make but we don't have a vaccine. So what we do is we treat people but we don't actually cure them.

If you'll take a look at malaria, the last drug for which there is still very little resistance is now encountering resistance and that drug was developed 2,000 years ago. It is an herbal medicine from China from sweet worm oil. Now, the Nobel prize was given to one of the scientists who understood the critical elements in the sweet worm that would be an anti-malarial, but think of it as a 2,000-year-old medicine for a condition that kills a million people a year. I'm sorry; at least 700 million to -- 700,000 to a million people a year.

And then let's think about tuberculosis, the classic diagnosis for TB is 100 years old. The ineffective vaccine for tuberculosis is 80 years old and the last medicine until last year, new medicine for TB was 40 years ago.

What is the problem? Why don't we have, with all the modern science, with the ways in which we can treat and cure cancer, why don't we have these solutions? And I'd like to just talk about three things that I think are critical.

The first is innovation. Now, that's a word that a lot of people use and it's an easy word that slips off the tongue. Every company has it in its logo, we're innovative. But what is innovation? There's a difference between evolutionary innovation and revolutionary innovation. If -- I'm a gastroenterologist. I used to treat lots and lots of people with peptic ulcer disease. All of the treatments had to do with reducing acid. So first there were antacids, basically alkalide that you took. Then there were -- there was a Nobel prize given for the first antihistamine, Tagamet that caused lowering in peptic acid. Proton pump inhibitors became a product that sold \$14 billion a year, the biggest product class in the world, but none of those cured ulcers because the day you stopped taking the medicine, the ulcer came back.

And what happened was some outside-the-box thinkers, revolutionary innovators came up with a theory that it was an infection that caused peptic ulcer and if you treat the infection the ulcer goes away. And sure enough, that's what's happened. And why do I tell this story in Global Health? Because it turns out that the same infection causes gastric cancer, and if you look in -- the largest cancer burden for the poorest people in the world is gastric cancer, if they can live long enough to get it.

And by the way, this didn't cost a lot of money. In fact, these scientists couldn't get money for their idea because all these ideas are subject to peer review and true innovators have no peers so therefore you cannot get an innovative solution funded. It's very hard to.

One of the great things about the Gates Foundation is that we had enough money and we had a kind of spirit that allowed us to make high risk investments. You heard about that a little bit from Trevor, but we were willing to do that and we had a program called Grand Challenges Exploration that focused on true innovation, outside-the-box thinking, rewarding creative thought, not preliminary data. I think we need much more of that to get solutions to problems that have been around for a long time and we still don't have solutions for them.

Now, the second thing that's needed for success here is the pharmaceutical industry. You may or may not like the pharmaceutical industry, but nobody makes drugs except pharmaceutical companies. That's a fact. People think the NIH makes drugs. They do not. They make the science that goes into drugs but they don't make drugs. And I learned all too well when I went from academia where I had millions of dollars of NIH funding, to industry, and learned that all I knew was the smallest part of making a drug, the basic science. There's a lot more critical applied science that goes into making a drug and that can make or break a creative scientific idea.

So how do we get pharma companies involved? Well, it's a tough thing to do because they have to answer to shareholders. They have to make a profit. Your pension probably depends on their profit along with the oil companies and hopefully not tobacco companies, but companies that make a profit. And so how do we engage them? Well, one thing that we can't do is to engage them, engage their committed spirit and then ask them to -- ask them to go bankrupt because if without intellectual property they will go bankrupt. There is no way they can make a profit of hundreds and millions of dollars of investment unless they can get a return on that investment. But there are ways and there are creative ways that you can incentivize pharmaceutical companies.

I can talk about two that I've been part of. One is called a priority review voucher. Now, the priority review voucher, essentially we worked on this together, Hannah, it was a brilliant idea by a couple of professors in a business school at Duke who thought that the way we could get some investment, in their case they were thinking about anti-infectives but became more broadly to apply to products for diseases of the developing world, and more recently to orphan diseases for children, but the idea was that if you made a product for a disease for which there is no market in the U.S. and which had a significant impact on the global disease problem, then you would get a priority review voucher.

Now, what does that mean? It means that you can apply this voucher to any drug in your portfolio and that drug will get a review in six months, whereas the standard review is 12 months. Does that seem like a lot? Well, the pharma companies, I couldn't convince them that this was a really valuable property, okay? They said, Oh, you know, our best estimate is \$20 million, maybe \$10 million. That's all they saw. Well, I can tell you what happened. The critical proof of concept was when Sanofi purchased a priority review voucher and that allowed them to launch a new product, multibillion dollar product in atherosclerosis a couple months ahead of Angin. They would have been four months behind. In fact, they were two months ahead.

Now, what does this mean? Well, if you're first in class you get roughly 50 percent of the market. If you're second in class, you get roughly 30 percent of the market. Think of that for a multibillion dollar drug. How many billions is that worth for a drug during the course of a lifetime? So you can see what's happened now. Actually the price of the first PRV was \$60 million. The last PRV to sell was \$350,000,000, and these dollars went to small companies who are making products for global health. And the big companies saw that that was a tremendous incentive for them to actually acquire the asset because it would bring profit to the rest of their portfolio.

This kind of creative idea is really important. I won't talk about the other one because I'm running out of time. But I want to talk about a third very important issue. Making medicines costs a lot of money, lots of money. The Gates Foundation was a 50/50 partner with GlaxoSmithKline in making the first vaccine for malaria. It's not a great vaccine, truth be told, it's maybe 50 percent effective. This drug cost us \$750 million. How many products can we make if each one costs that much, and where is that money going to come from? The Gates Foundation is rich, but not that rich.

So how do we get this money? Where do we get not 100 million here or 50 million there, but billions of dollars to create new medicines for HIV, malaria, TB, pneumonia, diarrhea, all the things that we can think about that kill children? Well, the only way is if people understand that global health is a matter of national and global security, national and global security.

This is what happened with HIV in America. HIV in America was sought to be a disease that sinners got and so there was no interest in it. When it became something that could be brought in from outside to the United States, then big money came available in a program called the President's Emergency Plan for AIDS relief, and that program was a multibillion dollar program, and where do you think the money came from? It came from the Department of Defense budget because it was a national security issue. And when you think about Ebola or you think about H1N1 pandemics or SARS and you see what happens to a small country like Singapore when SARS occurs is that the airport closes, the borders close. Nobody can travel. The economy tanks. It is a national security issue.

And so when we can think about global health problems as true national security, global security issues, then we can tap into the budgets that will give us billions and not millions. Thank you very much.

[Applause.]

MS. LARSON: Hello there. So that was a very nice presentation. Thank you. And thank you, Tony, for being the scientist because I am not a scientist nor am I an IP lawyer, but I've been at the Allen Institute for quite a while and we are all about openness and so that is why Dick has me on the panel. So I'm Maja Larsen, I'm the general counsel at the Allen Institute. These slides were put together this morning so bear with me. There could be a couple typos.

So I want to talk about the Allen Institute and who we are and how do we balance innovation management with being as open as we are. So we started out as the Allen Institute for Brain Science back in 2003 and we started with \$100 million of seed money from Paul Allen and we are still primarily funded by Paul. He has committed about a billion dollars at this point to the Allen Institute. We are a nonprofit independent medical research organization and we're focused on doing basic research to propel -- well, the brain science side is focused on propelling basic brain science forward, fueling discovery to move brain science forward as quickly as possible. So on -- and we call -- we say what we do as "big science" because we do everything on an industrial scale.

Our mission is to deliver all of our data management and tools as open as we can to the research community and also to the public and the way we disseminate most of our data is through our website. So the first 10 years of our existence was basically creating atlases of gene expression in different models. We did the mouse brain, the human brain and the nonhuman primate, the cat brain, for both the adult and the developing models. But once you got all of your models -- all of your atlases done, you're kind of done making atlases, making mops, and so in 2012 we launched a 10-year plan to really dive deeper into brain science and ask some more hypothesis-driven questions, to ask some of the big questions around just figuring out more about the brain. Like how is it built, what are the parts, how do the parts talk to each other, how do the parts -- how do the parts receive, store and pass on information, and most importantly, what goes wrong in disease.

So you'll notice the underlined words and that's important for how we are balancing our openness with our innovation management. We are -- it was easy for us early on particularly to be a poster child for openness and open science because of our funding. We are funded by primarily one single philanthropist who has a passion for open science.

We are doing basic research, so on the development cycle we're at the beginning stages, so we are doing all basic research, which doesn't have a lot of patentable, you know, protectable things as much. And our mission is to propel science forward, so our mission is to get stuff out so that we can make science go faster. If we spent all the time protecting everything, we wouldn't be able to get that out as fast as we can.

In fact, when we started, we -- one of the things that we did was to put all of our research results out as soon as they went through QC, and between two and three times a year, we would put out our research results, and we were told that we would never be able to get a high impact journal if we were to do that because we would be -- we would be putting out our research results. But it was more important for us to get out the research results than it was to be in a high impact journal so that's what we did was put out those results.

As it turned out, our first journal was the cover of Nature in 2007, so that seemed to be just fine as well. But that wasn't our purpose. Our purpose was to get it out -- to get those research results out. So because of our funding, our mission and where we are in the development cycle, it makes it the perfect Trifecta for us to be able to be open science and be the -- and -- well, to be the example. So, but you can see starting in 2012 we're now starting to think in terms of disease. So as we start to grow, that becomes an issue as to how we now have to start managing innovations.

So last year Paul gave \$100 million to create an organization called the Allen Institute for Cell Science. It's -- we're now called the Allen Institute and we have two operating divisions, the Allen Institute for Brain Science and the Allen Institute for Cell Science. Cell science is also funded right now -- well, 100 percent by Paul Allen, and it is focused on studying the cell as an integrated system in order to push disease-related research forward. So it's much more focused on disease-related research than our brain science has ever been.

And just -- but just like the Allen Institute for Brain Science, its mission is also to make all of its data openly available, all of its data, knowledge and tools openly available through open science. And the first project is called The Animated Cell. It's going to be a dynamic cell and it's hopefully going to accelerate cell biology and biomedical research.

So here is the evolution of our innovation management program, and we call it innovation management as opposed to intellectual property management because we think all of our innovation because -- it's a cultural thing. So as we've been growing -- so when I started, well, eight and a half years ago, there were less than 100 people and there were only 10 Ph.Ds. There's now over 100 Ph.D.'s and over 300 people and we're -- our trajectory is growth. And as you can see by the 2012 change in our 10-year plan and then the cell science, we have definitely grown in complexity. And that is required that we have to start looking at innovation management instead of just putting everything out open. And so we've had to start thinking about a policy and thinking about a program so that we're not just doing things willy nilly because that's not the way we do things. We do things very methodically.

So our mission has stayed the same. It's accelerating the pace of -- now it's science worldwide as opposed to just brain science and cell science and -- but our biggest mission is to make an "impact." And we use that word, we use it a lot and it is extremely important to us because that's what we measure. We measure our impact and we focus, we do things because of our -- to make the impact. We also use the word "stewardship" a lot because we are blessed with having an enormous amount of money for our research institute. And -- but we have to be good stewards of that money that we receive so we can't just give everything away for free unless that makes the most impact and is the right decision, but if there are ways to make bigger impact we should be using the resources that we receive to make that big impact.

So I get asked this question a lot, and as we're starting to go down this innovation management process, what about our big open science? And it's still our bedrock principle. We will always put out our data free and open up on our website. We are completely open access to Dick's point about being open access. All of our data is available on line. Not only our data, but also tools in order to read our data is also on line. And we actually do teachings. We have trainings all over the world to teach scientists how to use our data in order to get our data used more and more.

But where we have changed is the second bullet, and that is there are some things that are going to take more than just publications and database and data access in order to make that big impact that we want to make. And those are the things that we're now putting under the innovation management policy.

And as I've always told the scientists, open is never free and unrestricted. Even open source software has some kind of license. So it can't just always give everything away for free. There's always going to be some restrictions.

So I hesitated putting this slide up because this is so at the very early stages of what we're thinking of in terms of a policy, but actually I wasn't going to have any slides, I was going to speak to this whole thing, but I thought it would be a better visual to actually see it. So as we were going

down the pathway to figuring out how to make a policy on how do we care about innovation management, we started with our mission, which is accelerating science, and as you can see, we want to maximize the total impact of our big science research for the public benefit and also minimize the barriers of access. Those are the things that are important to us. And -- but now we're putting that parenthetical including entrepreneurial and commercial activities because we're now getting into things that we very well could have activities and we don't want to just say no.

We used to say we'll never patent. We don't say that anymore. In fact, we filed our first provisional patent almost a year ago. We don't know what we'll do with it. It's all baby steps at this point that we are truly practicing.

I got to talk fast. So when we would patent is when we would maximize public use and benefit. That's really the reason and we can talk about it. I won't talk about everything else but at the very end that's the most important thing. Obtaining the revenue stream is not going to be a priority for us in patenting. That's not even on the table for us. Our goal is to get our innovations out. So this is kind of what we create, that big -- that big part of the triangle actually should be bigger than that because most of what we create is data, but we also create software and bio materials and equipment and devices. And then we have other things that feed into data when you deep dive into our data. And those are things that we can figure out different ways to disseminate and that's really what is under our innovation management program.

So these are all the different ways of -- that we can disseminate, and this is the way when we talk with our scientists, these are -- our No. 1 way is through the website and publications. It's still our No. 1 way of disseminating any of our research results because that's, well, it's easiest and we hope that that would make the biggest impact. But we can also go through direct distribution and we do. We send out a lot of transgenic mice. We've got viruses deposited. We also do a lot of licensing.

And the last thing now that we're putting up IP, we can do patents, and again, it would only be if we're going to maximize public use or benefit. Or the other reason is if we want what we're calling "a seat at the table." And what that means is if it makes sense for us to spend the money to patent something so that then we would have something to negotiate with, that makes sense to us because that could make a bigger impact. So we would do that.

We haven't yet. We're still in the baby steps, but that's what we're kind of thinking of right now. Again, all of these are so draft slides that I wasn't going to put them up but it was easier.

So this is my last slide. We are blessed by being one of the only research institutes that have the -- in both policy and practice, that we can unequivocally be both open and practical. So we're in this place. We have this opportunity to lead and that's what we're trying to do with this openness. We understand that not everybody has that perfect Trifecta but we do. So that's it.

MR. WILDER: Thank you.

[Applause.]

DR. BLAU: So it's estimated that in the United States every year there are probably about a million people with cancer who get treated, and they get treated and they respond and are cured, or they're not frequently, and collectively we're no smarter for those experiences. And what we're aiming for through this entity that we created at the University of Washington called The Center for Cancer Innovation is that every cancer patient's experience adds to an ever-growing body of knowledge that makes us progressively smarter about how cancer works.

This started several years ago. I'm a hematologist. I didn't start off working in cancer, I'm a researcher primarily, but in discussions with my wife, who's a hard core breast cancer oncologist in private practice, maybe about seven years ago now, it became clear that we needed a

fundamentally different approach to address cancer. The condensation of the problem is that technology improves exponentially whereas the manner in which that's applied to cancer patients improves, but linearly.

So if you're in the position of a patient with cancer who's fighting for your life, you're facing an ever-widening gap between what's possible with technology and what's actually brought to bear in your care. And I think the grand challenge of our time is to find a way to close that gap.

So toward that end, we began at the University of Washington a clinical study, clinical trial about two years ago that is based on the idea that you would place patients with cancer at the center of an unprecedented scientific investigation. We have focused initially on a type of cancer called metastatic triple negative breast cancer. About 15 percent of all breast cancer falls into this triple negative category, and if you have metastatic triple negative breast cancer, that's thought to be a uniformly fatal disease. It's incurable.

And so we find women who have this incredibly difficult problem who want to be the subjects of an unprecedented scientific investigation in which they allow us to biopsy their tumor at multiple different sites of the disease because cancer between every individual's unique, but within an individual the cancer is constantly evolving so the tumor at one site won't be exactly the same as a cancer at another site.

We sequence multiple independent bits of the tumor, creating in some cases terabytes of information, enormous amounts of information, and we place it on the cloud and we make it accessible to some of the best computational biologists in the world who help us look at it, try to understand it to the best of our still meager abilities, try to synthesize it and look for a point of vulnerability that we might be able to attack with a drug. So within each patient, trying to make a prediction and then working very hard to make it possible to test the prediction in the patient. So if we think the patient might respond to a drug, and this may be a drug that's not approved yet, it might be in clinical trials or it might be approved for another type of cancer but not breast cancer, we put an enormous amount of energy in not only generating the hypothesis but testing the hypothesis in the patient and using what happens in the patient then to create a learning loop. Feed that information back to the computational pipeline and repeat the process iteratively over the course of the patient's disease so that we create a longitudinal analysis of how the disease responds within the patient. If we're wrong in our first guess, we come back and we try again.

And this has been a tremendously uplifting experience. You might find that an unusual description, but it's been a remarkable experience in which thus far 12 patients with metastatic triple negative breast cancer have made a heroic contribution to science by allowing us to study them to try to help them to the best of our ability, but also to use their experiences to help future generations of patients. One of the really interesting things that's comes from this is that when you do this in a single patient you get an enormous amount of data and you have to figure out how you're going to approach this. We commonly find that a mutation in a patient's tumor will involve a gene that we know to be involved in cancer, but the specific way in which it's been altered hasn't been studied, and so we have entered an area of the unknown.

In these cases we have found the world's experts on this gene and have contacted them to say: "We have a patient with cancer. This person has a mutation in this gene where you're the world's expert, could you tell us what you think about this? Could you tell us if you think this mutation will affect the function of this protein and do you think that this might make the tumor susceptible to a drug? And if so, what is it?"

And we've done this dozens of times and almost 100 percent of the time the researchers will answer and they will tell you everything they know, whether it's been published or not. One

of our most interesting examples was a case in which I sent an e-mail to a colleague at the University of Washington who forwarded my e-mail to another colleague at UW who in turn forwarded my e-mail to a researcher in Lawrence, Kansas who turned out to be the world's expert on this specific problem, and made a recommendation.

And so what that's led to then is the idea of trying to aggregate this knowledge so that -- and so emerging from this is a platform, a web-based platform where we've placed our patients de-identified information and make it open to anyone whose input might be helpful to our patients. And this has been built now in a way to scale so that this platform can accommodate hundreds of thousands of individuals.

Looking toward the day where, what I used to say was that if I get cancer someday, it would allow me to have my tumor studied on a molecular level, compare my tumor to those of a million other people with cancer, figure out whose tumor among those million people mine most closely matches, which treatments they received, what worked for them and what didn't, allowing me to benefit from that knowledge, and then have my own experience add to that knowledge. And as it turned out, ironically about six months ago I found out that I do have a form of blood cancer called myeloma.. And I'm doing great, but -- and now I'm the poster child for this approach where I am one of the patients on our web platform but -- along with patients from our clinical trial.

But we will be expanding this within the next few months to accommodate any patient with cancer who wants to upload their information and have it made accessible for global expert comment. And that's it.

MR. WILDER: That's good.

[Applause.]

MR. WILDER: So we have about 15 minutes left; is that right, for this session? I did want to open it up to questions from the audience but I thought what I would do is, as you're formulating your questions, maybe I can pose one to the panelists, including myself, and I'll answer it, do you think Dick Wilder is a smart guy? No.

[Laughter.]

MR. WILDER: I wanted to kind of go back to a couple things. One is the -- you know, it seemed like from what I understood of the discussion this morning is that there were some, you know, more fundamental questions that were raised about the role of intellectual property in the context of the work that we're talking about here in terms of developing and bringing to market new pharmaceutical products and pricing and so on. And I don't want to, you know, revisit that discussion, but -- and it did also allude to the fact that 70 years ago now there was some work that was done by Vannevar Bush in this country that kind of kicked off a lot of thinking about funding and participation of different entities in research in development, including the health sector, and also kind of gave rise to some of the legislation that we have in this country and still use today like Bayh-Dole and so on. And just raise the question of, well, 70 years on, you know, given where we are now in the world, should there be some fundamental rethinking about some of that? And I'm just raising the question.

But the specific question I had is, you know: Given all of that, you know, do you, the participants on this panel from the different perspectives that you gave, you know, if you look out into the world of intellectual property and licensing and so forth, see that in order to further your mission you think it would be better if there were some fundamental changes or revolutionary change, Tachi, in your remarks around innovation? And I can say that from the foundation, and I didn't really get into the details of it in the slide, but, you know, from our perspective is that we're comfortable using the current system of intellectual property. We have these very specific

discussions, again, at different stages of development as to what we need from our perspective in terms of global access and development, and ultimately bringing products to market and price and so on. And, you know, we've been very effective using the intellectual property system and managing it, managing licensing, again, to get what we want and to, you know, be sure that the companies, the universities and others involved are able to reserve, you know, their rights that they think that are important outside the scope of what we do and in particular where they think it might provide them some commercial advantage.

So we're not, you know, at a point in our work where we're -- and as Trevor indicated, you know, in the context of data and some other areas, we have some problems and there are complexities and we do have protracted negotiations and so forth, but at the end of the day they're not systemic, they're more specific to the projects that we fund and engage in.

So that's my question is just to see, you know, from the panelists, if you're looking at the world from your perspectives and saying there is something fundamental that needs to be changed either in, you know, the laws and regulations or the institutions that are involved in the work that we do. And as I said, from my perspective, from the work that we do, we're able to work in the context of existing norms and systems.

DR. YAMADA: Yeah, I don't think the issue is so much an issue of intellectual property as the issue of what you do with it. You can have intellectual property and not -- choose not to exercise it, and of course, that's what I think, Maja, you're talking about. Intellectual property can actually protect your ability to operate in a space where others might take that intellectual property and block people from doing things. So I personally don't think intellectual property is the fundamental issue. I do think pricing is a big issue, and let me just talk about the difference between the U.S., Europe and Japan when it comes to pricing. It's very interesting.

In the U.S., the price starts high and every six months, in some companies every four months, the price goes up, just keeps escalating. There's no control over it and there is no real competition in a way. In Europe, the price starts low, probably inappropriately low from the standpoint of the share of the R&D costs that should be borne by wealthier nations and stays low. In Japan, I think there is a very creative approach to this which is the price generally starts closer to the U.S. price, not as high as the U.S. price, but every year the price by -- every two years by mandate the price reduces, so you get your return on the investment you made but every year you get less and less of the profit.

They've created a new system, they call it sakigake which is a system that says, if it's really innovative, it's really going to transform human existence, then you can start with a high price and stay high. Okay.

So there is some element of reward for true innovation and that's very important. The reason why I say this is because a few years ago, I don't know what the number is now, but a few years ago the FDA's put out a study that said the average percent improvement in benefit over placebo of all the registered medicines was 10 percent. That's amazing.

On the other hand, if you take a drug like Sovoldi, now Harvoni, this became the poster child for pharmaceutical excess, \$84,000 for a six-week course of treatment. And everybody said this was outrageous, a thousand dollars a day. Well, this is the only drug I know of that actually cures a disease, cures Hepatitis C. And it not only cures Hepatitis C, but it prevents you from getting cirrhosis and liver cancer. To me, that's -- when you're counting all that up, that makes a lot of sense.

But if you take a cancer drug, the average cancer drug now launched -- is launched at about \$10,000 a month, \$120,000, and the average extension in life for that \$100,000 is about two

months. So there has to be some sort of value equation on the innovation, on the impact, on the true transformative impact to the medicine in setting a price and allowing the price to go up or down. Intellectual property I don't believe is the issue.

MS. LARSON: So I think we would -- we clearly don't practice in this field yet, but we would also be very comfortable that -- I agree that we -- the reason that we would be using it is so that we could control it and not -- and be able to get our research out the way we wanted to, so I don't think it's an issue.

DR. BLAU: And I think in the cancer space, lots of institutions are aggregating their data. It's not just cancer but in health care in general, we try to look across, you know, ideally hundreds of thousands of patients, find trends that could lead to interesting insights. But they're closed systems. You have to be either a part of the institution or part of a consortia of institutions. What we're trying to do -- and I don't think you need a different rule. What we're trying to do is just go directly to the patients who give us the information in hopes that it could be helpful to them, but then, you know, potentially bypassing all of that to get large data sets.

MR. WILDER: Thanks. So if there are questions from the floor, we have a couple of minutes yet actually before we break and take a couple of minutes and get set up for the second panel, but I did want to give, you know, folks in the room a chance to raise questions.

AUDIENCE MEMBER: I am really curious about what the Allen Institute's expectations are in terms of openness by the people who are taking your information and data, and do you see a voluntary mechanism and using intellectual property do you think you could sort of enforce that the way the Linux open source system has the cost of participation you give your innovation back into the system as opposed to paying money?

MS. LARSON: So I'm assuming you're talking about our data, and if you look on our website, the terms of use are very simple but we have three requirements -- well, requirements. One is don't copy us, and what that means is more -- it's more don't copy the entire data set and then try to sell it. So it's actually don't commercialize it. Because we're giving it away for free so don't go off and make your own data set and then try to charge for it. So that's the first thing. The second thing is don't block us so that we can continue doing our research. We -- and the third is give us credit. So those are the three things that we care about in people using our data. We want people to use our data for commercial purposes. We want drug companies to use it. If it's useful, that's part of our mission. We actually -- part of our mission statement is that we produce useful public resources. And if it's useful, that is a big bonus for us. That's our whole purpose. So we don't really -- we don't have any -- we don't own anything that you would have created with our data. That is yours to do whatever you need to do as long as you do those three things.

AUDIENCE MEMBER: How do you enforce that?

MS. LARSON: Well, the first -- so from the don't block us, so far we haven't had any issues with that, so I guess we don't affirmatively go out and try to police it like we would a trademark or something. And acknowledgment seems to -- again, we don't go policing it. We seem to get acknowledgment for when people, they understand. And the commercial use, people seem to understand what the commercial use is. We actually, we've had to clarify that in the terms of use because people have used our pictures in textbooks. And a lot of our images and they've used them in textbooks. There was a woman who created a training for -- using the Allen Brain Atlas and she was selling the training, and so in those instances, what we do is we -- well, to the extent that we can divvy it out, we did on the terms of use and just said any textbooks, please do that, we don't want to give you a license. For the woman with the training, we just gave her a license. That's isn't the intent of what we're considering commercial use.

AUDIENCE MEMBER: Do you have to like agree to the terms of use or something to get access?

MS. LARSON: So there's no click through. So it's pretty loose. We haven't -- we haven't had any issues to date. As we are -- as we continue to grow up things might change, but given that our philosophy is so open, we're not going to have a, you must click this in order to see our data. That is -- that would be completely counter to the way -- to being open.

AUDIENCE MEMBER: So one question in terms of a second element: Did you give consideration to the partly more aggressive approach which is not about blocking us but about blocking anyone?

MS. LARSON: Don't block anyone.

AUDIENCE MEMBER: Meaning that anybody that's using --

MS. LARSON: I don't know that that's the way it's written. That's an interesting point. I don't think that's the way it's written but I like your point.

AUDIENCE MEMBER: In terms of the mission, what it does it then creates a platform - and you know, that's what the --

MS. LARSON: Yep.

AUDIENCE MEMBER: -- the new and all those do, so it's that whole continuum in the software space. So just curious whether you --

MS. LARSON: Didn't even think about it.

AUDIENCE MEMBER: Okay.

MS. LARSON: But good point.

AUDIENCE MEMBER: Thank you for the presentation. I have a quick question for -- I don't know if it's quick, but for Dr. Blau. The work that you're doing, do you run into barriers I guess from a regulatory standpoint when you're sharing this information on patients with clinical experts or experts? Do you run into any regulatory barriers, privacy barriers, and finally U.S. payer barriers when there are treatments that may truly help these patients but then the payers may balk because the experimental nature of the medicine that you're looking at?

DR. BLAU: Right. We spend a lot of time on is the patient confidentiality issue and HIPAA compliance laws. We've surveyed the 12 patients that have come into our clinical trial about how important is it for them to maintain their confidentiality. And the vast majority don't care. They find the benefit of potentially being able to access experts that they have no way of accessing otherwise to be overwhelmingly more important than protecting their confidentiality.

Another safeguard that we put into the platform is in order to come on as a contributor or somebody that wants to look at what's going on, you have to agree not to attempt to learn the patient's identity.

As far as regulatory issues go there are huge burdens associated with trying to get drugs. So in three cases where there were investigational drugs that we wanted access to, we were able to do it but we had to do it through single patient clinical trials, single patient INDs. Each one requires an enormous amount of work. In one of our patients we had a pretty strong lead suggesting that a particular drug might help that patient, and despite enormous effort with the company to try to get access to that drug, which is in a Phase III clinical trial in lymphoma, we were not able to access the drug for our patient. Despite the fact that the drug company was planning a clinical trial of that drug in triple negative breast cancer that they would have done in nine months from now, we couldn't get it for her. So that's -- that's also a huge hurdle.

PROFESSOR ROIN: Just real quick, this is just something I've been curious about lately. So one of the problems I've noticed with data management in the social sciences is the

interoperability of different data sets. So you've got one data set collected one way, another is collected another, and you want to know a question and you need both the data to answer, how do you get them to speak together? It sounds simple but it turns out to be paralyzingly difficult in like most of the time I've seen it come up, but are you guys trying to deal with that in some way? Because you're both like collecting data for other people to use and then also using different data sources, is there some sort of effort in this biomedical space to make the -- a collection or a presentation or use of the data so it will speak to one another or is that just something that like people are aware of but don't have an answer to yet?

DR. BLAU: It's a huge barrier, but there are many companies and other institutions that are working to aggregate information across different electronic medical records. Creating structured data out of PDFs presents a very significant challenge. It's something that we spend an enormous amount of time on trying to make sure that the data that we collect can be interrogated when it expands to thousands or hundreds of thousands of patients. It's a hugely important issue.

MS. LARSON: For us, we're involved in a number of initiatives for neuroscience data because it is also a huge issue. We -- one of the things we're focused on, because again, with our funding and where we're trying to go with the openness, is creating these usable platforms. So we have a number of initiatives, Neuro Data Without Borders, that are around the world trying to create some standards for at least the neuroscience data. But to open data access in general is just a big hairy issue.

MR. WILDER: Thanks. I think we have one more question.

SIR JACOB: It's not exactly a question. But I read last year that the British National Health Service launched a program of getting patient consent to all their medical records, which in due course, as it builds up will be an open access system for in effect the world. It can be the largest personal database in the world. I don't know how it's going or what's happened to it since, but more generally, you said with your 14 patients all said, Of course.

And the truth is that this confidentiality business of medical records is probably causing more trouble than it ought to and the way around is, I think, a default consent position that when you go to a doctor, you consent unless you withdraw the consent. Much the same as they're just trying in Wales for organ transport. Everybody in Wales now is taken to consent unless they've withdrawn it.

I think we should be moving that way for medical records of treatment because most people say, Of course. Say, I'm ill, and it's going to be good for mankind and of course other people can use this for that purpose. I think it's a great pity we're not pushing in that direction in some ways.

MR. WILDER: Would that be implemented through changes at National in the case of the European Union through regulation or would it be done on -- simply as a matter of practice by IRBs?

SIR JACOB: Well, the Wales thing was done by legislation at the Welsh assembly. UK is slightly fragmenting. It would have to be done by national governments. But you only need a few governments to change the position and you're creating a database for the world. If the United States did it, it would be fantastic. If the European Union did it and China did it, it would be fantastic.

DR. YAMADA: Without getting into a big argument here, I think there is an alternative point of view which is about privacy and the utilization of the data for many different purposes, for example, for employment or for insurance or for, you know, admission into universities and such. I think it's not a straightforward issue.

SIR JACOB: There's ways around that.

DR. YAMADA: We can spend two days talking about that.

MR. WILDER: Which we'll do at the reception later on this evening. All right. So thank you very much. That's it for our panel.

[Applause.]

[Recess was taken.]

[Concluded at 4:20 p.m.]

PANEL III
ACCESS TO MEDICINE: CHARITIES, ACADEMICS & INDUSTRY COLLABORATION FOR NEW
TREATMENTS

Moderator:

Dr. James Haley, *Ropes & Gray (New York, NY, USA)*.

Panelists:

Dr. Jurgen Dressel, *Novartis (Basel, Switzerland)*.

Yoichi Okumura, *Japan Pharmaceutical Manufacturers Association and Takeda
Pharmaceutical Company, Ltd. (Osaka, Japan)*.

Jerry McLaughlin, *AgeneBio Inc. (Baltimore, MD, USA)*.

Hannah Kettler, *Bill & Melinda Gates Foundation (Seattle, WA, USA)*.

MR. HALEY: Ladies and gentlemen, I'm going to have to inform you that Toshiko has said there will be no reception unless you get back to your seats. And she is very difficult on this point. But really, I know very well that I don't want to stand in the way of the reception and I've already told our speakers that anyone who goes over time will be subject of ridicule of all of you and you get one less petit four or whatever we're going to have at the Gates Foundation.

So the last panel of today is about access to medicine for new treatments. And obviously before you can have access to medicine you have to develop the new treatment or the new drug. And as we learned this morning, most of these repositioned or established drugs with new uses are discovered by academics, by clinicians, by happenstance, by somebody having an idea for a new hypothesis as to why disease works in a particular way and then they begin looking for drugs that might treat that disease.

So you often have the discovery of the disease and perhaps the new treatment. Now you have to find someone to fund it, to fund the development, to help you get to the clinical trial, to help you build your market. And the people who are funding who have the deep pockets are looking for how they're going to get a reward from doing that, and I think this panel is going to try to address that with some real life situations.

Jurgen is going to start talking about really what the problem is with skinny labels, which means a label that excludes the new use but the doctor is prescribing for the new use and therefore the development of the new use does not get the proffer to which he or she deserves. Yoichi is then going to talk about what Takeda is doing in Japan in particular models of various things to try to overcome this thing. Jerry McLaughlin who is the CEO of Agene that happens to be one of my clients, is really in the pits right now trying to convince someone to fund a clinical trial for a drug that may in fact delay the onset of Alzheimer's and having a lot of trouble because it's an established drug. And then Hannah is going to talk a little bit about how the Gates Foundation funds this type of research. So I'll turn it over to Jurgen.

MR. DRESSEL: So good afternoon, everybody. I'm not as tall as Jim, therefore I stand here on the podium. I don't know how you guys feel this afternoon after having heard these people from the Gates Foundation and the Allen Foundation and what I have to say, I feel inspired. I also feel humbled. Now -- and I have to say what I should say is I would like to thank Toshiko and Dick and especially Robin of actually putting such great people together and tell us about these alternative ways of how we possibly can fund research into pharmaceuticals.

As I said, I feel humbled. You know, I almost hesitate now to go back into the nitty gritty details and to the mundane world of enforcing patents, but I decided I have only this slide deck so I will do it.

[Laughter.]

MR. DRESSEL: I'm sorry for that. So how did we get into this strange situation? We started out, in principle people found, yes, this clinical innovation should be patentable. They granted many patents for it, and now suddenly that we are trying to enforce this patents, we find out hmm, maybe they are not really worth an awful lot. Isn't that a strange situation? So let me try to take a little bit of a historical perspective here.

When you look at TRIPS Article 27.1 says you can basically patent anything under the sun as long as it's novel, inventive and has some industrial application. There are very few exclusions there, and one of them says you can exclude from patentability methods of treatment.

Some countries actually decided to ignore that. US, Australia are countries like that as it comes to matters of treatment, but some -- many other countries actually, decided yes, I want to make use of that exclusion. So when you look at the latest version of the European Patent Convention, Article 53c , Exceptions into patentability, one of them that is excepted is methods of treatment of the human body. But there's an exclusion in the exclusion and that actually was one that was introduced after case law had actually made it possible to patent clinical innovation, methods of treatment -- not directly methods of treatment but some of you might have heard these weird animals of Swiss-type claims. And they basically want to legalize that and put that into the statute and therefore they have this use-limited product claims, the exclusion of the exclusion.

Maybe it's worthwhile thinking again why was there actually the first exclusion? And a little bit of insight is given by an Enlarged Board of Appeal decision. That's the highest Board of Appeal at the European Patent Office, so just a few snippets from that decision G-2/08 which dealt with dosing regimes, and there were social, ethical and public health considerations. There were physicians who should be free to take all actions they consider suitable to prevent or to cure disease and in this exercise they should remain uninhibited by patents. What happens if you have a patent on the compound. Of course, as a matter of principle, you could actually prevent the doctor from applying that where there's no exemption for the doctor to practice what he does.

So I think the exclusion of the exclusion we saw earlier makes a lot of sense in that context, because the second medical use is not so much different from the first medical use of the component as such.

So then how did we run into the current predicament? Let me talk about these terms "carve out" and "cross-label use." This is a typical picture you probably have seen many times. The pharmaceutical company spends a lot of time and money to do research, development and regulatory approval for the drug, and very early on you actually file a basic compound patent, possibly extend it depending on the country where that is possible in order to take account of the time you have to spend for the regulatory approval process and for the clinical trials which take longer than for other technologies.

And then as you are actually developing your drug, you actually learn more about the drug. You get more experience and you might actually have the idea, maybe it's not only for the first indication but another indication B where it can also be used. And sometimes you get a patent on that, the so-called second medical use patent for B.

Traditionally, in most countries a generic had to do a one-to-one copy of the label of the originator. So it had to contain all the approved indications, A and B. Of course they could get to

the market after the last patent of the second medical use patent expired, but not, strangely enough, when the first indication A was in principle patent-free.

So you see the tension. You see a little bit of an evergreen element there. And the legislator said something had to be done about it, and he asked very early on and had already contained the so-called carve-out possibility. So carve-out of B led to a so-called skinny-label generic, so a generic that does not contain all the indications, but only the patent-free indication A, not the patented indication B was perfect.

And that's fine, so as long as they only come with indication A, the patent-free indication, that sounds fair. But the problem came when actually most of skinny-label generics in the marketplace were used cross-label for the still patented indication B. And that seems wrong.

Let me explain a little bit. I can explain what I actually mean by cross-label use because it's not such a commonly used term, but I find it useful in actually distinguishing from the normal off-label use you might be more familiar with.

So what's the difference? When you have an originator drug, and let's say it's approved for those two indications, A and B. When that drug is used for those indications it's on-label. When - - but sometimes you find maybe an indication, or there's some scientific evidence where the doctor says, Okay, I can also use it for this other indication C, that would be called off-label use.

Now, let's look at the skinny-label generic. The skinny-label generic has carved out the patented indication B. Then the skinny-label drug is used for this indication B, in principle it's not really an off-label use because the drug as such has been approved for B. It has been approved in the originator label. And therefore, by cross reference to the originator label, the skinny-label drug could be used for the carve-out indication. That's why we call it cross-label use, this is a different kind of animal. Yeah, because when you look at the early case law or the determining case law in the U.S., for example, a lot has to do with off-label and not a cross-label situation.

So just to give you an example of how the market works, the pharmaceutical market is relatively complicated. When the physician prescribes the drug in Germany, he usually prescribes it by the INN, by the International Non-proprietary Name, and he does not specify the indication for data privacy reasons, for example. And then when a generic exists, the pharmacist is actually forced by agreements with the insurance companies to take the cheapest one. And then since the pharmacists don't know the indication, every now and then they will dispense the skinny-label generic for the patented indication. And of course the insurer doesn't mind. He prefers to actually reimburse it for the cheaper price.

So now we have to look at the incentives. Is it then actually worth it to develop the drug for the indication B when you don't have any meaningful exclusivity for the second medical use? I on purpose enhanced this -- you know, when you look for the details of the blue arrow, I enhanced it by exclusivity because maybe the patents are not the only thing that you can actually use in order to get exclusively. Maybe there's some other form of exclusivity you need, but it will heavily depend. Each pharmaceutical company's decision to actually develop a new second medical use will be heavily dependent on how much exclusivity is left.

And in that situation, I've seen -- I've actually experienced situations exactly like this one, where it basically eats up all the 20-year term and the only thing that is left is the maximum of five years' patent term extension. Where there's already a question mark, should we actually do it? Does it make sense to spend these hundreds of millions of dollars in order to develop these drugs for this new indication?

You can imagine, the longer it takes, the less likely this will happen and here I put a big question mark. I think it should be a no. It will simply not happen. When there's no exclusivity left

and the one for the second medical use patent doesn't really give you a meaningful exclusivity, it simply won't happen.

So here, this is one example which a colleague sent to me which I find a little bit personal, it's a little bit emotional. You see it already from the title, The Shameful Story of Rituximab in Multiple Sclerosis. But it was a blog published in a Neuroscience Journal of Immunology and had quite a few comments, as you can imagine. This is actually worthwhile to look at this one because I think it illustrates the predicament quite a bit.

So the story goes like that if you follow this blog. rituximab is an antibody approved, among others, for rheumatoid arthritis. In 2010 the Phase II clinical study was published for this drug for MS, so for a different indication, and it was as efficacious but with much less side effects, and when you look at MS treatments, they have quite a few side effects, than the standard at that time. Actually this clinician who wrote this blog said it was revolutionary.

But the patent expired in 2015 and no Phase III trial was done yet, and guess what the originator did? They didn't do the Phase III study with rituximab -- is that real? minutes do you want?

PROFESSOR TAKENAKA: Yeah, but how many

MR. DRESSEL: 15 I said originally. You haven't told her yet, huh?

So they took a similar drug with the same mechanism of action. They actually came up with the same efficacy, but a much higher mortality.

So the conclusion of this clinician is that this is terrible. We don't have so many choices to give our patients to throw away the best ones or to have to wait several more years. And I think that's exactly the predicament we are facing, when we don't give an exclusivity that would actually justify it.

So without business certainty and incentive, of course, we as originators, we have a problem because we won't invest in this type of R&D. But it's not just industrial originators, it's also academia and a lot of this innovation is actually happening at hospitals. The patients and the physicians will have less new therapies available. The health care systems, they think short-term very often nowadays, but they should think long-term, yeah. Because usually the drugs actually save money. And of course the generics, it's not good for them either because they get smaller markets in the end.

So I think carve-out is fair. The skinny-label generic should be able to get to the market, but cross-label use should not happen.

So my last slide. We are talking about a complex and very heavily regulated market, and unfortunately there are systemic incentives for cross-label use. So you have the short-term budget pressures, everybody is complaining. The health care systems, the insurance, yeah, they want to reduce their expenses. You have a burden when you actually talk to a general practitioner. There's a court trial, for example, ongoing in Europe, which is making headlines. For the physicians it's awful, yeah. They have so many things to think about, should they have to think about what type of pregabalin they should actually prescribe when they have these other things also on their minds.

Incentives for generic substitution I already talked about. And in principle, the insurers, yeah, they get away with it. There's a relatively low legal risk until now. The second medical use patents have been largely ignored.

The therapy exclusion squeeze, I talked already a little bit about. I think it's fair, but the doctor doesn't really suffer from what his freedom to prescribe the best drug for the patient, because he can choose the on-label originator drug. And I think there's also a role for the courts to play. I think it's important that they don't stick to the literal wording of the Swiss-type claims, there should

be a purposive claim construction here because the purpose was really to stimulate clinical innovation, so any result leading to not stimulating clinical innovation I think would be the wrong interpretation. Thank you.

[Applause.]

MR. OKUMURA: Maybe five minutes. I am Yoichi Okumura of Takeda from the Japan Pharmaceutical company from Tokyo and today I'm really so happy to be here and thank you very much. Toshiko required me to be here to, actually she required me to be here as a sort of representative for Japan Pharma industry. That's why -- my name tag said the Japan Pharmaceutical Manufacturers Association but the company is Takeda anyway.

I supposed to go through these so many but with five minutes, maybe one minute each. I'll try. Okay. This slide is showing the, how to say, the current pharmaceutical industry's new movement. For example, development of new compound requires large development cost, so many companies go into the repositioning of the existing drugs. Because existing drug already have been approved based upon their safety and efficacy as well. And also the blockbuster type drug business now goes away and turns to sort of the gene therapy or precision medicines. And the small molecule business is now going to be replaced with the biologics and also the regenerative medicines. Okay. These things, how to say, make us think about how to protect our future business with IP.

And then what I have to say about secondary patent is that the secondary patent is very important vehicle to build up a business with new technology. So importance of secondary patent was already discussed early in this morning session, that's why I do not touch on it so deeply.

Okay. Let's move to this one. This slide describes IP protection of the secondary patent and the use patent in Japan. Mainly, as most of you already know, medical treatment method is not patentable in Japan. There are lots of reasons but I do not touch on all today. One of the reasons is, according to the Japan patent law, that this medical treatment method itself is outside the scope of the industrial applicability. It is one of the requirements for the patentable invention.

Then -- in recent Japan the translational medicine type of disease treatment has expanded. In that sense the precision medicine, the regenerative medicine and the genetic diagnosis type of research and also its therapy & drugs are going to be popular. It means that medical treatment method itself of physician is now getting closer to the industry activity. Previously just drug was a drug but medical treatment was treatment by physician. You did somehow separated them in different categories. But these new technologies make industry activity much closer to the medical treatment.

Then how about in other Asian territory? For example, China and Korea, in those countries there are lots of uncertainties. Sometimes they allow those secondary patents, and sometimes they give low patentability to the secondary inventions. In India as all of you know about 3(d) problem. That's why almost no chance to get the patent right in India.

But recently the TPP fortunately generally was agreed among those countries. That was good. Member countries of the TPP are required to protect secondary patent. That's our hope.

From the next two slides I have to show the important activity in Japan, e.g., regenerative medicine which was made by, as you know, one of the popular professor at Kyoto University, Professor Yamanaka who won a Nobel prize. That is the iPS technology. That is pretty much important to science for the entire Japan now. My company also just has initiated a collaboration with his laboratories.

But looking at the regenerative medicine, it's very tough to imagine what kind of things or processes can be protected by the IP by the patent system. For example, some cell, maybe almost

the same as a natural cell. Some cells are derived to be somehow closer to the natural cell. And then some other cells can be derived to the totally artificial type of the cell. Maybe this green type of cell can be protected by the patent but we don't know how yellow and this different type of the cell. We can't expect to protect these inventions by the patent system.

Then among those technologies we may need to also consider about FTO issue because there are lot of technologies, complicated ways of combining together especially for the manufacturing technology. That's why we may need to think about sort of the forest of the patent rights. It has been discussed in sort of industries on those types of things.

And the next one, this is technology from the Tokyo University, venture company, Thera. This company providing sort of the combination therapies of these standard therapy in cancer vaccine therapy area. They are providing license to the hospital and also they are providing sort of vaccine or tube to the hospital. This is their new business model.

In this kind of business model, an issue is how we can protect this new business model by the patent system. This is the most important item that we are going to think about seriously in the future.

Then I need to touch with somehow access issues. Actually let me back to here. We have been considering just the patent for protecting of the technology, but I would like to express that the patent itself should be sort of the vehicle for developing of a new business. Otherwise, patent system would mean a sort of just domination of our technology and it would also give its negative impression of society. Actually, if we can obtain this patent protection in emerging market, we could expand our business in those areas, but without any patent system and protection system of the business, then we cannot bring our business to such society. That means even if we get the new technologies, new invention, those cannot be expanded noe distributed to many of the people who need such them in the emerging market. That's why we really like to maintain a patent system in an emerging market. Maybe only in LDC of Least Developed Countries, maybe they might not need such protection. But even in those countries they need to improve themselves to catch up and to be the next better level. Then they need a patent system. That is sort of the key for the access issue for the emerging market and also the LDCs. That's it. Thank you.

[Applause.]

MR. McLAUGHLIN: Well, it's been an interesting day in that as we've talked about new uses for existing drugs and the debates and the challenges, my stress level goes up and down with each talk because I'm right in the middle of it. So this is a case study in progress for a new use for an existing drug and before I get into it, I have a little preamble. And this is born in academia and one of the leading neuroscientists in the word, Michela Gallagher at Johns Hopkins, she just received a lifetime achievement award for neuroscience and her life's work was really studying the neurobiology of the aging brain and that led to a discovery in the classic sense of basic research. And it just happened that the best target was an existing molecule. And it also just happened that the science around the understanding of the pathophysiology in the early stages of Alzheimer's was misunderstood for decades.

So you had that perfect combination of existing drug, if we had known about the mechanism in the pathophysiology, it would have surely been developed or attempted to be developed and there would have been IP around that. But because we thought the world was flat and then it was round, it created an opportunity. And so we'll talk a little bit about that, but we're going to talk about Alzheimer's a bit at first, and I think we all know this is, it's a tragic disorder that affects too many of us, too many of our family members and it's only getting worse. We all, I think, know the numbers, about five million cases a year in the United States that will go to about

13 million by 2050. Every 68 seconds in the United States somebody is developing Alzheimer's. It's costing Medicare and Medicaid, not with soft costs, just direct medical costs, \$250 billion and I think that's dated several years. So we're approaching the point where it's about a billion dollars a day that it's costing our government in direct medical costs.

So we know the most common risk factor is age, so every day we live on the planet we're at more risk. And that really has interesting implications around the world and we'll take a look at that in a second. Here is the -- every dot represents 100,000 cases of Alzheimer's. Good news for Alzheimer's, we didn't live as long back in 1950 so most people died before they developed Alzheimer's. As you can see, in 2000, a lot of growth. The scary point coming up here and please look at the difference.

By 2050 there could be 90 million cases of Alzheimer's in the world. And it's not just a disease of the developed world. The developing world is growing quite rapidly. The African continent will quadruple in Alzheimer's cases over the next 35 years and if the Gates Foundation does a great job, unfortunately it's going to be worse for Alzheimer's because, once again, age is the No. 1 predictor of Alzheimer's.

And you see the implications in India. India, China and across Southeast Asia, it's really astronomical. And here are the numbers. This is dementia. About 70 percent of the cases of dementia are Alzheimer's, it's the most common form of dementia, and that's where we get the 90 million patient number by 2050.

So I'm going to ask you to step back. When you think about Alzheimer's there's a classic case of we think about the dementia and we think about the saying of not being able to remember a child, the loss of functionality and eventually death, right? Forgetting how to eat. But it starts much better than that and that process of the dementia stage is typically around seven to 10 years. But there's also a seven- to 10-year process prior to that which is called many things, it's pre-dementia Alzheimer's, prodromal Alzheimer's and the FDA labels it right now, aMCI due to AD, which is amnesic mild cognitive impairment. So you're not in a demented state, you're functioning, but memory is fading rapidly. And that could be diagnosed easily with the patient and typically with their loved one. And this is affecting about five million patients in the United States today and will double by 2050 if nothing is done.

And as with the case with many diseases, there's been a lot of attempts early on and where the treatments exist are for the Alzheimer's/dementia. There's symptomatic treatments, they work in about half the patients and work for about 18 months. The disease continues to progress, the drugs no longer work, and then there's nothing left to do. But we're learning now in this new age of Alzheimer's drug research and discovery is that we attack the disease early prior to neurodegeneration, or when there's minimal neurodegeneration we have the best chance of either stopping the disease -- but at least, if we can change that trajectory ever so lightly, it can have a major impact on the overall prevalence and the overall health care burden. And we see this here.

Unfortunately, there's nothing available today in this predementia stage of Alzheimer's. Everything that's been attempted has failed. The existing therapies not only are not approved; they've been proven not to work in this stage of Alzheimer's. And you can see here, this is an interesting study that was from the Alzheimer's Association, if you can bend the curve, shape, change the trajectory, if we can delay that conversion from this predementia stage of Alzheimer's by five years, we can reduce the overall prevalence of Alzheimer's dementia by about 43 percent.

The bigger issue is you're avoiding a lot of end stage Alzheimer's where 24-hour care is required. And so that's where the big impact on society is and that's why we have so much focus by governments around the world on doing something about Alzheimer's.

And so this gets back to sort of the genesis of we're not just a reformulation, what we're developing, it gets back to what I was talking about, the basic science, but the question was: What if what we believed to be true for decades was no longer true, and this is the case here and a part of the pathophysiology of Alzheimer's that led to the development of our drug candidate, and so here there's three basic lines. One is amyloid. Probably everyone knows what amyloid plaques are. And they're associated with Alzheimer's. Every patient with Alzheimer's has an amyloid plaque on the brain. Not every patient who dies with amyloid has Alzheimer's, but that's another story for another day.

But that precedes the disease state, a lot of ramp up in amyloid, and then it's always been known, or at least for several decades, that you then have a period where the area of the brain called the hippocampus. The hippocampus and the internal cortex, this area of the brain, are responsible for creating your memory. And this ramp up in activity was well characterized, well known. It was believed to be compensatory or beneficial.

And it kind of makes sense, right? You have a brain that's starting to atrophy. You have memory decline. Let's ramp up neural firing and activity. That's beneficial. That was the belief until as recently as 10 years ago and it was highly debated in the literature and now -- we now know and it was based upon the work at Johns Hopkins and then subsequently repeated at Harvard and UCSF and other leading centers around the world, that this ramp up in hippocampal over activity is in fact a primary driver of the initial stages of neurodegeneration in Alzheimer's. It results in atrophy of the internal cortex, is where we process new memories, recent memory.

And then eventually you see the hippocampal activity just phased out as you have tremendous cell death, atrophy in the hippocampus and the internal cortex. And this is important sort of in the drug discovery here.

So we call it repurposing a drug. We like to think of what we're doing is reinventing a drug, and I'll lead to this. I saved my heaviest slide for words, but so we have novel science. What we are developing is known as Keppra, it's from a branded sense. It's levetiracetam, it's an anti-epileptic that's been available since 1999. Sold over \$2 billion in the U.S., more around the world. Great product, great molecule, very clean molecule. But it was never pursued for age-related cognitive impairment because what does it do? It subdues neuronal firing in the hippocampus which in epilepsy you want to knock that down. And it was always believed until recently that in Alzheimer's you don't want to knock down that activity, you want to rev up activity.

So the basic work that our founder did in her age-impaired rats and saw the correlation between this ramp up in hippocampal over activity and memory loss. We repeated this time and time again, we repeated it in UCSF in a different model, and then the big step was to go into Phase II. So lo and behold we have Phase II clinical data. Along the way that would show that if you deliver a low dose of this levetiracetam, you actually can attenuate or mitigate minimize this hippocampal over activity and preserve function in the internal cortex. Fabulous work.

So along the way we're developing IP and my IP attorney counsel assures me that it will withstand anything, but the patent office is not buying this because they're saying UCB had to have thought about this, had to contemplate. This is subject a big market, there's five million patients in the U.S., maybe 25 million worldwide. This has to be obvious.

Well, it wasn't until we actually showed up with our Phase II clinical data, and I'm saving a piece of the data for you here in a second. What we demonstrated, and it's up here on the slide, the adult dosage for epilepsy is one gram to three grams per day, and that's why they never saw results. But what Michela had found at Hopkins in her work was she started at microdoses and moved up, she found that there was this dosage range that was subtherapeutic for epilepsy, between

125 and 250, that was effective for age-related cognitive impairment. It restored balance to this network.

What we also found in all the animal models was, once you moved above 250, no effect, no impact whatsoever. No different than the placebo using -- and we replicated that in human clinical trials. When that data was presented to the patent office, they finally gave us the seal of approval. They said, this is not obvious, this is truly novel, and we were issued a method of use patent that gives us a coverage around a dosage range that today is subtherapeutic, okay?

And what we like about this, we have a novel disease state from a protection, right? Method of use -- there's differences in method of use patents, and you can speak to this better than me, and we have the authority sitting next to me. But we have a novel disease state. We have a unique dosage level that previously was not therapeutic, and then we have clinical data actually to support this that shows that dosage range.

And then we continue to build out the IP, right? It's not lost on us that we have a reformulation. So we continue to build a picket fence strategy around from an IP perspective. We've developed a novel proprietary formulation which we built some protection within there as well.

The question came up here on this panel was about funding and it was discussed this morning. And I agreed with all the points that were made earlier today, and to date its sort of been a little bit of this and a little bit of that. Prior to my joining the company it was truly high net worth individuals, the classic friends and family. One of the things we did, we added an additional board member when I joined and that gave us access to a network of high net worth individuals which I would advise anyone here starting a small company, it's a great source of capital.

In addition, Johns Hopkins has been very generous, both with time, resources, and then as part of the deal when we created -- when AgeneBio was created, they were willing to convert the accounts payable in intellectual property to equity, which in a small company is very, very beneficial and very important.

In addition, the company has been supported through NIH grants, multiple NIH grants. One paid for the Phase II trial, another is paying for a lot of the work in our -- we have also the discovery stage program. The NIH can be very supportive early on. Also, a foundation such as Alzheimer's Drug Discovery Foundation. They paid for our extended release formation. We sent them in a proposal for the project and they like to -- they have to know what the foundation wants to support; they like to support finite projects over a finite period of time. They helped us develop our formulation. And then additionally, like I mentioned, we had high net worth individuals.

The big step forward and what Jim was alluding to is now it's time to raise the big money, right? We're in the Alzheimer's field. Our study will cost around \$90 million which is on sale for Alzheimer's. You hear Biogen spending a billion and a half dollars on their Phase III program. Merck's phase number studies, we hear they're upwards of 200- to \$250 million to trial. So we're cheap from a standpoint but it's a substantial amount of capital and it's very different than friends and family.

That said, there are many opportunities to raise that capital either through partnership or through a hybrid approach, through private equity and also family offices. It's a lot of work, as was mentioned this morning, but there are unique family offices that have particular interest in this disease state because the only thing -- they've been able to control everything in their entire life, have all the money in the world, but they can't control what happens with their brain and they want to see something change in their lifetime.

So that's where we're going for now. I will mention here just everything everybody knows, but if I've heard it once, I've heard it a thousand times in my life in the reformulation world. There's this classic bias of as soon as you hear reformulation, low level of innovation -- and nothing could be further from the truth as we've talked about today. If our therapy works in Phase III and can be on the market to slow the progression of this predementia stage of Alzheimer's, I would consider that exquisite innovation.

And there are some who just won't look. There are companies who will say, we only look at candidates with composition matter. Just as a rule we don't look at method of use. We're never going to change their minds. Same with some investors, and then the assumption is, We'll get around. I know you have Jim Haley from Ropes & Gray but we'll find a way around his patents.

And then there are the patients who will not sufficiently reimburse to 505(b)(2). I think that really depends. 505(b)(2) is a term, don't blanket it as uniform. There's 505(b)(2) where you take a twice-a-day formulation and make it once a day. That I think is some level of innovation but I put it on the low end. I think what we're doing here is taking an unmet disease with five million patients in the US, maybe 25 million worldwide, providing a novel dosage for them in a disease state where we could major implications. I consider that pretty high level of innovation.

And I did just have a conversation because I said, Enough of this. And we're doing some research now on reimbursement. I talked to the chief medical officer at Express Scripts, I was at a conference, and I made a beeline for him at the break and I explained to him our profile and I was very honest with him about what it is and what it is not. And he says, Well, we're looking to help treat Alzheimer's. Everybody wants to do that. And I said, Yeah, but are you going to engage in pill splitting -- with each dosage form it's 220 milligrams once a day and there's nothing that can there exactly.

I said, are you going to engage in that? And he goes, we don't want to do that. That's not our business, but if you get greedy we will, and his message was, Don't be greedy. And don't -- like some of the things we've heard in the news recently, don't try and take too much, right? We'll pay for the innovation even if it's a reformulation but keep it within reason.

And I think that's a reasonable approach. Now, we'll continue to do more work, but we think there's a way to navigate through this and that's what I'll ask you to leave with, don't blanket all reformulations as the same color. So with that I thank you.

[Applause.]

MS. KETTLER: Great. Thank you. I know I stand between you and the reception, but I'm proud to have an opportunity to speak to you. It's actually the first time I've ever had a chance to hear Trevor Mundel and Tachi Yamada speak together at the same meeting, and so it was a real privilege to hear that and just how different, but also how inspiring both of them are as we think about solving these critical problems in global health.

Tachi mentioned that he was worried Trevor might have spoken to the things he was going to talk about. Well, I had Trevor, Tachi and Dick all ahead of me, and in fact you all covered what I was going to speak to, so I will cover some key issues and hopefully we'll still have a little bit of time for discussion.

So my agenda. Specifically, I'm going to look just briefly at how critical innovation and in particular -- whatever, reformulation, repurposing, incremental innovation, just kind of all types of innovation, how critical that is for the success of our mission at the foundation. And then I'm going to give the example from the neglected tropical disease work, and if you stick around you're actually going to get to see the results that Trevor is really excited about. So that's your carrot for sticking it through to the end.

So as was alluded to in previous presentations and as you will see when you get to go to the visitor center, fundamental to the foundation is the concept of every person has the right to a healthy productive life. All lives have equal value. So in that context, the foundation is very focused on trying to develop and deliver and impact health issues that affect predominantly the poorest in the poorest parts of the world.

A concept that we are working on, and it's actually been a learning process I would say, is how important it is that we think about development in the context of delivery. And that seems obvious, but I think when we started there was a real premise; as Tachi alluded to, there were no vaccines, you know, we need drugs, that if we built anything people would buy it and it would be used. And so there was a real focus initially on the product development piece of our business. And over the last five, six years since Trevor joined and then we also have a new president for delivery, we have a much firmer focus on trying to bridge between what -- what's the infrastructure, what does the world look like that we're actually working on products for and how do we think about that when we develop new products.

So Dick alluded to our global access agreement, he didn't just allude to it, he actually documented it. Really critical to access is not just literal affordability, it's also is it available enough at a sufficient scale and is it appropriate? Does it work in the regions that we're talking about? And accessibility in this case also means can you get it there. So is it deliverable infrastructure, et cetera. So with that in mind, and then you think about the global areas that we're working on, the diseases we work on, modifications of products are fundamental potentially to the success. If you think about HIV, HIV drugs, the idea that we have no vaccine so we are trying to advocate and expand treatment, well, we've got an adherence problem and -- we have an affordability problem but we also have an adherence problem, so the increased focus, for example, on long-acting intellectual virals is necessarily building off of the markets that we're targeting.

Pediatric formulations, children under five are fundamentally a focus of ours -- our work, so pediatric formulations. Fixed dose combinations, trying to get products out of the coal chain, oral formulations when you have injectables, et cetera. So again, really critical that we have an environment that motivates and incentivises companies and organizations to think not only about novel, but also about potentially combining and modifying existing drugs.

I'm going to focus the rest of the talk specifically on the neglected tropical diseases and -- just because background, and this was something that Trevor referenced and you can think back to his slide of all the bubbles with sizes. The NTDs were all along the bottom, they were the smallest circles. Together they do impact building people and there's a lot of vulnerability to getting, and NTDs tends to bundle. Here's the diseases and they're hard to pronounce. I couldn't spell them. It may finally be spelled correctly. These are really challenging diseases people haven't heard of, and as I say, on some they impact millions and billions of people but they tend to be forgotten because they're relatively small and exist really truly in the poorest parts of the world only.

So the question is: Can you get more visibility to these diseases and then what can we do to try to address them? And back to Trevor's question of, Well, what do we work on? And you might say, Well, these bubbles are really at the bottom of the spectrum. And again, I don't have the slide to reference, but even new products in this area, it was kind of borderline whether they were cost effective or not. But the good news is that there's a real expectation, and they also reference this: That we might be able to do something about this, that impact is really feasible.

And in 2012, in an effort to bring the key partners and stakeholders together, the foundation, together with 10 of the largest pharmaceutical companies, many of you in the room,

your CEOs participated in this event. It was a bringing together of the private sector, the WHO, the World Bank, key donors, the Gates Foundation, with an eye of creating a coalition that would commit to try to work towards what are very ambitious goals of four diseases eliminated by 2020, two diseases eradicated by 2020, a whole host of regional elimination achieved, and that really depends a lot on the availability of product as well as the availability of funding.

And so -- but there's a lot of optimism, and one of the reasons there's optimism is the availability of treatment. So -- and I don't have the time and actually am not the world's expert on this so I really couldn't speak to it anyway, but there is a history of pharmaceutical companies donating drugs for many of these diseases. And what's interesting, and this is just a short summary, and again, many of your companies here that -- many of your companies are here on this list, all of these drugs were developed for something else. Many of them were actually developed for the veterinary business. A lot of these diseases are worms, parasitic diseases and there is overlap with the animal health world. So that was the incentive to develop a lot of these.

A couple others are antibiotics. The Gilead product I think is the only one that's still on patent. Everything else has been off patent, but initially there was a real opportunity to make the money back you needed to for the research and development and even sustaining -- continuing to sustain manufacturing, but also at the same time, donate. Once it became clear and, you know, the community of researchers, people who -- and this is truly just pulling together those who are motivated, individuals who are trying things out in the field, aligning some facts with some of these drugs and sorting through that they might work. And if we have a chance it would be really interesting to hear a story from one of the companies -- we don't have time, but just kind of the history of how you came to the side.

I would flag, there was a reference to the Artemisinin Nobel prize, there was also a Nobel prize given to two researchers who together are given credit for the discovery of Ivermectin which is a drug that Merck donates for onchocerciasis and LF. So the success of the coalition and the achievement of goals is very much resting on the generosity of the pharmaceutical industry, but it isn't donations for everything and it is also true that these had a business case and a business model that worked to allow donation to be possible.

So now, one fact is also true is that although we have most of the tools that we need, we don't have everything, and this gets to what Trevor was speaking to which is the idea of a macrofilaricide. I'm actually very grateful he spoke to us because he's a much articulator -- I'm an economist, I'm not a scientist, so you actually already got the version of why this is so exciting and what the problem is. But essentially for both lymphatic filariasis and onchocerciasis, we have drugs that work for the baby worm, they kill the baby worm, but you have to then treat people who are exposed to these worms every year, you have to get back to them and treat them every year. And there's an approach to treatment called mass drug administration where you basely give everyone who's anywhere near the possibility of getting this disease, every year you try to get ahead of it.

But none of these drugs help with the adult worm, and without killing the adult you're not going to be able to achieve the goal of elimination. And so the foundation, at the same time that we're advocating for more funding and looking to give as much credit as we can to the pharmaceutical industry for the donations, at the same time we're doing that, we're also looking for ways to try to bridge this research gap. And both of the ways we're looking at solving it fall very squarely within the terms of this conference and the meeting -- the discussion you're having.

One, again, Trevor gave a really good description of is the idea of repurposing, so trying to figure out -- we only have until 2020 in theory and so we have to get going and that's not a lot of time, trying to see whether you can't find something that already has clinical data just to test for

safety -- to confirm for safety so that you can actually move things faster forward. And the other is the idea of testing drugs that you already know is safe. As Trevor alluded or mentioned, these drugs have been used -- billions of these drugs have been used, how can you bring them together in combination?

And so this is the data, and again, Trevor referenced and it is really exciting that bringing the combination of -- so Ivermectin is a drug donated by Merck. DEC is a drug donated by the Japanese company Eisai. And I want to give a little credit to Eisai separately because it's the only company -- all the other companies had a history in these diseases and these drugs and the CEO of Eisai was motivated to get involved. They were the head of IFPMA, and so in 2011, they made a decision they wanted to do something. And one of the gaps that were identified by the WHO was insufficient availability of DEC. And they actually invested in developing DEC, getting it registered, building a manufacturing plant so they could give it away. So that's exceptional level of generosity. Everybody else has a long history with this drug, they're the only one, so I give a little bit of extra call out for them.

And albendazole GSK donates. And so the standard of care is DEC plus albendazole except in places where there's also onchocerciasis. And the study that was done was to try the combination of all three, and again, the data speaks for itself in the sense that when you just use only the two, you get kind of a mixed spread of clearing, whereas with the three, you get 100 percent. And also Trevor mentioned that this holds for one year. It also holds for two. And so we now necessarily have to scale up beyond Papua New Guinea and there is a lot of looking into how do we get new trials and new studies on to this combination to make sure there's no adverse events that would prevent us from scaling it up.

But again, the great news is, companies are already donating these drugs and with one exception, where we'd need them is where they're already donating, and what that means is hopefully we'll be able to leverage their preexisting commitments and scale things up really quickly and in fact get out of it faster. So it's win-win for the companies in the sense that they won't be donating for as long, and for us obviously to get rid of the disease. Just to give you an idea, and again, it's tricky for onchocerciasis regions, but again, not to go into the details of that. These are the key countries that will potentially benefit from the scale up of the triple drug and that has a huge impact on and helps make significant progress towards the goal of elimination for lymphatic filariasis.

So in closing, I just want to reinforce, it's been a real privilege to have a chance to speak and just the real relevance importance of solving the problems that you have raised for the Global Health. I want to acknowledge -- actually I'm an incentive geek and I'm sorry I didn't have a chance to participate in that piece of the discussion. Just a closing comment that the priority review voucher that Tachi was really excited about, one of its limitations for all of this that we're talking about is it will only be rewarded to new products. So it can never be previously approved in the U.S.

And so interestingly, in its current formation, it actually does not serve as an incentive for what we're talking about here, and yet, given that it's a relatively cheaper exercise, in theory at least, to get some of these incremental changes made, a voucher of this type would actually potentially be a really perfect way to get it done. So with that I'll close. Thanks.

[Applause.]

MR. HALEY: So I think we have a few minutes for questions. Maybe I'll start off with one for Jurgen. You discussed the idea of this market issue in trying to avoid off label versus cross label. What type of law or legislation would be required? How would this be put in place?

MR. DRESSEL: I think in principle what we need is something like a market segmentation where the different indications are clearly separated from each other. And I actually found what was said I think by Stefano this morning interesting, yeah, where basically the reimbursement by the insurers depends on actually if there's indication on the label. And the Japanese, they have such a system. It has been softened up a little bit, but in the past at least that worked perfectly.

So basically there was a system where the doctor actually had -- he didn't put the diagnosis indication on the prescription but he had to supply it to the reimbursing party and they basically compared what was dispensed with what was actually the indication it was prescribed for. And that worked pretty well.

MR. HALEY: And Yoichi, you proposed some changes in the patent laws. What would have to happen in Japan to do that?

MR. OKUMURA: Changing the patent law in Japan?

MR. HALEY: To cover cells, for example, in your examples.

MR. OKUMURA: Oh, that -- actually so Japan patent rules have to be changed anyway, Therapeutic method should be patented and protected. But if -- I don't know how to say, such new, protection could make us, how to say, be able to bring big innovations in the future in the pharmaceutical fields.

MR. HALEY: And Jerry, could you give us a sense of how hard you've had to work to try to get somebody to fund your trials?

MR. McLAUGHLIN: As they say, it's a big bite and a lot of -- and we face a number of challenges, not just related -- IP is one. As everybody faces challenges. Alzheimer's disease is considered a high risk category from a development standpoint, given the -- everyone saw that article where 99.6 percent of trials have failed. And I guess we're that 0.4 percent. So that raises a challenge. So I think the bigger challenge is around, you know, it's an equation, right? It's not -- it's never a simple answer, it's IP, it's reimbursement, it's cost to get to market, right? And so it's a formula and everybody weighs each differently. And it's just finding the right mix. And I can say, though, while some -- and we talked about this, some will never entertain a reformulation. Others see the value. They see the risk mitigation. I can tell you, it's in our notes from the FDA from a pre-IND meeting. They said, "No additional nonclinical safety studies will be needed, the safety database you generated with a single Phase III will be sufficient to file."

I don't know of too many NCEs that would ever have that that in pre-IND meeting minutes. So there are some tremendous risks we take out with novel uses of drugs, particularly in this case of being a low dose.

MR. HALEY: How about in the audience? Any there questions in the five or six minutes we have left? People are hungry.

MS. KETTLER: I just want to make a comment about a funding mechanism that the foundation has established, and I'm actually sorry that we can't fund your Alzheimer's trial, but one where they try to balance. So we've got -- we made a contribution to something called the Global Health Innovation Fund and it's a combination of for profit investors and the foundation and other nonprofit foundations, and it's kind of a fund where there's some preparedness to take a double bottom line approach. There's an expectation of return, but within the fund itself, the nonprofit are the ones that take funding last and the for profit get the funding first.

And so in general, that pool needs to be targeted on sort of charitable products or products that advance the global health mission, but there's a real recognition that there's global health products that also have commercial return. But I only offer that as potentially a benefit that those who have more or less risk coming together and funding Alzheimer's.

MR. HALEY: So audience, any questions? Comments? I want food.

[Laughter.]

MR. HALEY: Well, then, thank you very much for attending the panel and thank you to the speakers.

[Applause.]

[Concluded at 5:27 p.m.]

PANEL IV
PATENTABILITY AND PATENT EXTENSION OF NEW USE AND NEW DOSAGE REGIMEN FOR EXISTING
DRUGS

Moderator:

Dr. Andrew Serafini, *Kilpatrick Townsend & Stockton (Seattle, WA, USA)*.

Panelists:

Shinjiro Ono, *Yuasa & Hara, Tokyo, Japan, Former JPO Deputy Commissioner (Tokyo, Japan)*.

Dr. Ute Kilger, *Boehmert & Boehmert (Berlin, Germany)*.

Robert Stoll, *Drinker Biddle & Reath, Former US PTO Commissioner (Washington, DC, USA)*.

Jin Ooi, *Allen & Overy (London, UK)*.

Hon. Peter Meier-Beck, *German Federal Court of Justice (Karisruhe, Germany)*.

PROFESSOR TAKENAKA: Good morning. Again, Toshiko Takenaka from the University of Washington School of Law. I hope that you had a good time afterwards, yesterday's session, at the Gates Foundation and of course we enjoyed our exercise at the Gates Foundation as well as the development as well as contributions Gates Foundation have made with respect to global health.

So today we will be focusing more on intellectual property, particularly patent law. Myself used to be a patent attorney and trying to enforce patents of Texas Instruments. I am very excited to hear from experts from the world with respect to the patent procurement first session in the morning, as well as the second session more to do with remedy.

So the first session is led by Dr. Andrew Serafini and I will let Dr. Serafini to take over that for you.

MR. SERAFINI: Thank you, Toshiko. Good morning, everyone, and welcome to the Pacific Northwest Day 2. I hope you enjoy the sunshine. A little housekeeping. Our esteemed panel will be talking, and if we can hold all questions until the end, we'll start with some questions directly here from the panel, and then we welcome actually as much participation as possible.

Let me start off by saying that the dilemma regarding second generation patents can be summed up in the words of the Federal Circuit in 2008 when they were overturning an award of horrible attorneys' fees against an innovator manufacturer seeking to enforce a second generation patent that was deemed invalid. And I quote, "While it may be considered more socially desirable for companies to seek truly novel inventions, formalities not yet treatable, the patent laws set the standard of novelty nonobviousness and utility as a requirement for patentability without making value judgments concerning the motives for making and attempting to patent new inventions of lesser medical value."

So the patent laws embrace attention between the public interest and the ideals of investments and profit. Ultimately it is the patent laws and patent law jurisprudence that must guide our judgments about the enforcement of second pharmaceutical patents in the battle over global drug markets.

So our esteemed panel, they're in the program. I will not introduce each and every one of them, but to start off we do have Shinjiro Ono from Yuasa & Hara to kick things off this morning.

MR. ONO: Good morning, everyone. I think -- most I think a right thing to do to the Japanese I think low end practice, especially related to this second medical use and patent extension. And I used to be I think an examiner and a peer examiner, a JPO, so I think the objective of the JPO are involved in their compiling of the examination guideline. And also I think there are lots of I think the drafts role related to our improvement of our IP system and especially patent system in Japan. Okay.

My topic will first touch upon the eligibility of second medical use, and I will introduce the background and also I think Japan is a very unique tried to I think to introduce their protection of medical treatment both I think their both medical treatment by a physician and surgeon by the patent protection like the United States. I want to explain a little bit of background.

I think that you see that their medical method is usually, I think except in the U.S., most of the country, all right, Japan and Europe and the other country, not considered as patent eligibility. Because of that, I think they are closely related to the doctors and promises and also I think the patient. That is one of our barriers. And these I think the medical treatment considered to be industry applicable. That is one of the I think methods.

And also I think most of the country now I think they're not considered as patent-eligibility, medical treatment. But I think, in Japan, I think the 2005 Phase-I in the year 2003 and 2009, we change the examination guideline, especially the first one is very amateur. So I think the Plan 2 protected medical treatment. This is I think there are just I will touch upon the background.

I think at that time in Japan, that year 2003, IP headquarter was set up directly to go the prime minister. That at the time I think Japan try to bury I think the strings in their IP protection. And two, I think there are Japanese inclination based on IP I think the asset. That is, I think the background.

Then I think there are -- first I think the main important issue is whether I think in Japan, is it possible to protect the medical treatment process? Of course I think there are promises to protect the and medical propriety is already I think the patent protection. But I think the medical treatment method is I think -- maybe I think there are people who are I think in favor of the strength of the IP protection is try to change asking us, the government, to try to change it at all.

This is I think the IP strategic program. I think the IP headquarters and giving master I think assignment to try to change the law. And this I think that we set up in group and consisting of many I think are broad range of people relating to not only the IP people but also the consumer and the doctors and also I think many I think scholars. Not only I think IP but also the rigamarole and many I think people gathering to discuss the possibility.

And before we are in Japanese situation historically, I think in Patent Act of 1959, I think is the old chemical substance and also medical drugs are not considered to be patent eligibility. It is forbidden. Like I think there's some different country, people that take trips, I think many countries, developing countries, not the chemical substance and drugs are outside scope of the protection. But I think 1979, I think that we I think changed the law to accept the chemical substance process and the drugs process to protect by patent rule.

I think that I would like to draw your attention to 1975. At the time I think Japanese pharmaceutical industry is behind in terms of R and D. It's not so strong now. There were lots of I think discussion. But I think that this -- I think that change overall were asserted in Japan. And at that time I think the medical I think is protected procedure are protected by the law in the form of I think their use limited product-type protection. That is very important.

I think now I think in Germany and in Europe also I think there are product type use limited product type protection is available for a drug. But in Japan, also I think first that we introduced

the changes of law over the same things, product. And we discussed under the walking group, I think there are pro and con and these I think there are lots of I think discussions. Politically it's very, very difficult. I think the pharmaceutical industry sending a request in addition to the protection product to protect the method process. But I think there are government one year I think the discussion. I think it's very difficult. Because I think there are -- this is the same as I think Europe. I think it's explained in the medical treatment per se is not industry applicable.

But I think -- one I think important the call to decision relating to this I think medical treatment, especially in the field of medical to recommend representation, surgical operations. But I think the past is patent protection. But how about the method of I think treatment by this device. But Tokyo High Court I think the JPO will deny that protection. The Tokyo High Court upheld the JPO decision. But I think the reason is I think the main reason is industry inapplicable. But I think the court raised the question why. I think there is no demarcation between the medicines and the medical devices and medical treatment.

What is the difference? One is I think clearly industry. But how about medical treatment? Even though a doctor I think doing, but what I think in the United States because it considers to be industry. But the court said that without any statutory measure to immunize them from the suit, their hope I think it is we called on it too. This is I think is industry applicable is okay.

Then this I think the politician discuss to try to change the law if possible. That is, I think the background of our patent group. And the conclusion is after one learns the discussion, I think very strong operation by the doctor's association, they said I think that our practice is not the industry because I think Japan is older, the medical treatment, I think all the costs will be covered by the universal, I think the national insurance policy. And also I think the doctors' role is to cure the patient. Not they are seeking I think any profit or something. But personally it's a question, but I think that that is originally is what they said.

Then I think the result is like this. I think the conclusion is I think as this, patent protection as an incentive to I think the industry is very difficult. There I think, instead I think the examination guideline is very important. Then I think -- first I think the examination guidelines I order to the person to compile. There are two approach. One is I think even though the medical method I think as long as the medical device is represented as a method, in that case I think as long as that method is not including the invasive, I think to the human body, it's okay. That's I think the drafting to that I think invention. And also medicine invention is, as I explained, they're protected other use limited to the product protection. And the medical claim of substances in Japan. I think that these are the same as I think the Europe. And you can read clearly and *understood the difference I think the three overall* differences.

And also I think this -- in this assumption guide, first we included dosing method in the interval is okay. Or that I think the medical medicine use applied to the specific I think to their patient group. But I think this is one of the examples I think.

Then I think that these I think are within the process examination guideline. Then I think after I think four years, I think the review of the IP headquarters again I think according with I think the development of technology, JPO tried to cover the more cutting edge technology, IPS and other combination of new technology by guideline. That is a matter of drafting technique without changing the law. And these are I think from first 2005 that you can see that the second I think specific dosing interval had remarkable effect on a specific group. These are no application because it's so limited. Then I think there are new their new guideline is not limit to the specific group. In general, I think dosing method is okay. And also I think the method for measuring structure or function of the human body is okay as long as there is no invasion to the human body.

That is, I think try to avoid doctor practice, it's okay. That is, I think the matter of drafting. These I think are present kind of situation in Japan.

And now I think this is an example of I think as long as very remarkable effect. I think at that time pharmaceutical industries trying to request us to protect I think these inventions.

One thing is whether these I think the new guidelines or protection compiled by the JPO is possible or not. Only one directly I think discussed, is I think this is Takeda and I think the Gyo-wa Company. I think this invention is a combination of medicine are already expired and combination -- well, I think have a remarkable effect. But I think this case is a little bit I think not good or I think example of what are called medical decision. Because I think this patent was invalid. The lack of effective step.

But I think that in the court decision, they said -- they tried to impose this method. But I think that -- I think the company tried to impose indirect infringement. But I think this is not I think good from my point of view. I think that the combination is try to I think of enforcement. It's better to see drugs in combination with. Direct infringement drug technique may I think solve this problem. I will not go into the details because I think the next session will cover this issue.

And then I think I would like to touch upon a little bit I think the most recent Supreme Court decision just rendered I think November, I think also two weeks ago. I think completely I think the change the Japanese practice relating to the patent term extension. That is, I think -- you can see I think this is a history of a patent extension in Japan. This is a little bit different from European SPC and I think the U.S. system.

First I think the 1987 the patent system was introduced in Japan. And first I think this law is not changed. And also guideline has been a long, long time I think in the use of the past guideline. But I think in 2009 I think there are draft system case. I think the guideline with I think some should be changed. And then second guideline. Then I think this second guideline was rejected by the Supreme Court or the High Court.

I think there are -- it's a very -- we are always thinking about this article at the time is I think an examiner, well, he should have a reason for rejection at this point. But I think -- this I think work I think used in the article is not clear and ambiguity. Therefore, I think there is room how to I think interpret this one. In Japan, I think there are first guideline is long. I think the scope of rejection and scope of extended patent is thin. Because I think there is active -- I think the scope of rejection is defined by the activity ingredient and indication.

And this I think the Supreme Court decision most recent rendered is I think a genetic case. I think this is an example. The first I think approval of one. I think the subject approval is I think this dosing method, this dose is I think the feature. Prior approval is a different dosing approval. And the JPO said deny this approval. Because of I think the same active ingredient and the same indication.

But I think this approach was denied because of I think the first approval will not lead to the marketing I think the present, this position by the authority.

Therefore, I think if you refer back to the original I think intention of the law, this should be I think protected. Therefore, I think the Supreme Court decided and also IP High Court rejected the JPO's approach. Then I think each time I think if the subject approval not covered by the prior approval, in that case I think the approval should be protected.

Therefore, I think the result is it's very clear in Japan every time I think the approval received, it is possible to -- as long as the patent is I think embodied in that case, I think the second approval and third approval if the dosing, I think the method will depend is also eligible for extension.

That is it. Thank you for your attention.

[Applause.]

DR. KILGER: So good morning. It's exciting to be here. There is a saying which says that a British speaker will start a presentation with a joke, but the German speaker would start with a table of contents. So I don't have a table of contents here.

MR. STOLL: That was a joke.

DR. KILGER: Oh, really sir. I didn't get that.

So although there is no table of contents, I would like to start with explaining to you the different claim formats we have in Europe for the second medical uses. So as you know, the methods of treatment are not allowed to claim under the European patent convention. And the purpose of this is that the medical practitioner should not be hindered to treat a patient.

So the patent offices and European patent office, they invented the so-called Swiss-type claim in order to give some protection for the invention of a second medical use but not to hinder the medical practitioner from treating patients. So the claim reads: "Use of compound X for the preparation of a pharmaceutical composition for treating or preventing a disease Y."

So it's a bit confusing because you have here the step or the feature for the preparation of something, but it's not a novelty conferring feature, the novelty conferring feature is the use. The Germans they have invented another type of claim which was "the use of compound X for the new therapeutic application Y." So under the new European patent convention, this has changed and now the so-called purpose-limited product claim replaces the Swiss-type claim. And now it reads: "Compound X for use in treating disease Y."

And for the time being and for the near future, we will see that these, both types of claims coexist. So you will have patents with this type of claim and patents with the other type of claim. And of course the question arises whether or not the scope of the claim will be the same.

So, the European patent office seems to think that the rights conferred to the patentee by the new claim category, the purpose-limited product claim are likely broader and in particular lead to possible restrictions on the freedom of the medical practitioner.

There's a citation in a decision of the Enlarged Board of appeal of the European patent office: "if deemed necessary, the freedom of the medical practitioners may be protected by other means on the national level", which basically means if there is a problem, the national level should solve the problem. The courts shall solve the problem.

And also there are other decisions from the Boards of Appeal from the European patent office where it is stated that it is not admissible to switch from the old form, the Swiss-type claim to the purpose-limited product claim because this would be an inadmissible broadening. So this gives the impression that this is another type of protection.

So you could take both views. You could think, well, this is just a wording and it should not mean anything else. It should just be the second medical indication, thus –it should have the same scope.. Or you could take it literally, and you could think about the wording in more detail and the Swiss-type claim had this feature "for preparation of" and as the medical practitioner would not prepare the medicament for using it, he would not be infringing where in the other case, maybe he could be an infringer.

So we will see what the national courts will decide, whether or not the scope will be the same with respect to patentability and/or enforceability.

So my next topic will be that I am going to talk about is a very German principle, that is the principle of manifested arrangement developed by the German courts, or you can call it evident preparation, sinnfallige Herrichtung in German. And this concept teaches that the medical use

claim includes both, the medical use itself as well as the preparatory work required to put the compound into a form in which it may be administered.

So this looks for some material manifestation in the manufacture of the medicament, the packaging, the label, which can be attributed to the new patented use of the drug. And this principle has been developed in landmark decisions by the Federal Supreme Court of Germany. And they said of course if you read such a claim, use of a medicament for treating diabetes, then on the one hand it can encompass nonpatentable use, which is the doctor who is using the medicament for treatment, but it also encompasses patentable uses, which is formulation, packaging, dosing in its ready-made package.

And a question may arise, what happens if you have the first medical use and a medicament is prepared in a certain way, and then you have a second medical use, but you do not change the way of packaging or dosing. Would that be patentable as well? And the answer in subsequent decisions was “yes,” patentability does not require that the use of a known medicament for treating a second medical indication involves the medicament in another form.

So these are all court decisions and you might ask why I'm talking about this “old hat.” Maybe because this principle of manifested arrangement still plays a role when it comes to enforcement. And I don't go into details because I know that the next panel will talk about that in more detail. But of course you can ask yourself whether this manifested arrangement would not only encompass packaging and labeling, but also advertisement and marketing materials and so on. And obviously the court in Dusseldorf has decided this question differently from the court in Hamburg, which just said that a drug may be already, by its production, in manifested arrangement for the use in the patent protected indication if it can be used without any further effort but only needs its assigned purpose.

So where does this go? We will see from the courts and maybe also from the next panel.

So let's go in more specific detail what you can really have in your patents or what your second medical use patents can be based on. Of course it can be a new indication, means another disease, but it can be also a new use within the same disease, which is a different mode of drug administration or new patient group to be treated, a different technical effect or a different dosage regimen.

So of course all of these have to fulfill the requirements of novelty and inventive step.

So I would like to go into more detail with respect to the three latter mentioned new uses. Imagine you have the situation where a drug X has been used in a method of treating a disease in all patients, but later on you will find that the patients -- not all of the patients respond to the medicament. You have responders. You have non-responders. And you seek to stratify non-responder and responder in order to give the medicament only to those who will respond. And you find a marker which helps to distinguish these two groups.

So think about the claims you could draft. Of course you start with the new claim format drug X for use in a method of treating condition Y, but then you have to specify the patient groups in more detail. You could say wherein the individual has said genetic marker Z - would be one option. Another option would be that you define the patient group by stating an individual identified as having said genetic marker Z, and a third option could be for instance the individual wherein it is determined whether the individual has genetic marker Z.

So if you think about infringement, you would like to catch the alleged infringer with the scope of your claims, you would like to avoid the latter format because you cannot be sure that the alleged infringement act would really encompass the step of determining a marker. Because it

could just be that the doctor knows from former analysis that the patient has the gene. So you would prefer to have the broader claims, the first or the second one.

But then the question arises if the prior art has been used as drug for all patients, would these claims then be novel at all? Because inherently, you have treated -- when you have treated all patients those which had the gene Z. And also if the marker has been known before because it's a marker for other users as well, like the blood group or so, then it could be that the marker has been identified before independent of the stratification. So would then the second claim format be novel?

So and I think this is something where the US point of view regarding inherency doctrine differs from the European different point of view.

So what does the European Patent Office say? We had a decision of the Board of Appeals and it was about the use of an antibody, rituximab, in treating a disease. And the only novelty establishing feature was that it was administered to a human who experiences an inadequate response to TNFa-inhibitor, meaning nonresponder to another therapy.

So the question arises because prior art was that you gave the same antibody to all patients having this disease. So would that be novel?

So the patentee has argued that the prior art has neither disclosed a patient subgroup which experienced an inadequate response to these inhibitors nor the successful treatment of this particular patient group. And the Boards of Appeal actually followed this opinion and said that the patient group of the claims is distinguishable over the patient group of the prior art document by its physiological and pathological status. And consequently, this represents a new therapeutic application.

So you could ask yourself, how could this be new if this has inherently happened in the prior art? The answer is quite easy. Because before the European patent office, you don't have the doctrine of inherency according to a very old decision of the Enlarged Board of Appeal. And they are of the opinion and still they are of the opinion that the decisive question is, what has been explicitly disclosed in the prior art or to put it in other words, the question is not what might have been inherent in what was made available to the public. The decisive question is, what has been made explicitly available to the public.

So under European law, such a new patient group and would be patentable. So maybe this would be different in the U.S.A. A different technical effect could also lead to a new use and second medical indication. Here is a decision of the Boards of Appeal. A use of a composition has been claimed and the composition shall be used for cleaning plaque and/or stains from human teeth. And the prior art was the use of the same composition for reducing the solubility of tooth enamel. And both uses have actually the same goal. They are aiming for prevention of tooth decay. And also here it has been decided it's a new technical effect and leads to a patentable invention.

So there might be different cases where such a new technical effect would be denied. For instance, if the new, allegedly new technical effect intervenes with a known technical effect, so this is practically the same, or if you just give an explanation for a technical effect, but this does not change anything, not the behavior of the medical practitioner.

So last example for new uses is a different dosage regimen, which can be patented. And here is another decision. And I note that Peter Meier-Beck will refer to this in more detail. This is a decision of a the Enlarged Board of Appeal and here in the treatment regimen, the only novelty conferring feature was that this medicament as used in the treatment by oral administration once per day prior to sleep. And the question was if this were the only novelty establishing feature, is

the claim patentable? And if so, could this feature, which goes into the actual treatment process, could this confer novelty to the claim? And the simple answer is yes.

So in former times, the German courts, they had some reservations against such pure dosage suggestions, but they allowed claims requiring that the medicament be prepared for said dosage. But they had reservation against these pure dosage suggestions. But the question is being these reservations still applicable in view of the law as in force since December 2007 and in more recent decisions of the Supreme Court, and we will hear about it later in detail.

So let me briefly summarize. In general, as well as in Germany as in Europe, various types of second medical uses seem to be patentable or are patentable, dosages, patient subgroups, further technical effect, administration modes. Then what you also can see there is "Further harmonization of the Interpretation of the law in Germany and Europe." This has not been always the case. Then, a question is scope of protection, has the old claim format the same scope as the new claim format?

And the most exciting questions, of course, will be the enforceability of patents directed to these new second medical indications and the interpretation of the scope of the second medical use claim which is evolving in the case law, in particular with respect to manifested arrangement.

Thank you very much.

[Applause.]

MR. STOLL: Good morning, ladies and gentlemen. First I'd like to thank Professor Takenaka for inviting me yet again to come back here and talk about issues that I feel very passionately about.

I come from this slightly different than some of the speakers yesterday. My career, my entire career has been in patent law. I'm not an economist or ethicist, but I do have some background in patent law and ended up as the Commissioner for Patents for a long period of time. And I'm going to talk a little bit more about the issues in the United States with respect to subject matter eligibility and the case law and the evolution in what's happening here in the procurement of rights as part of this discussion.

So let me start off by saying there are some several different areas that I'm going to look at. I'm going to look at the Pharma Bio area compared with the high tech area. And I'm going to talk about what's been happening here and where I think things are possibly going. But as you can see, there are brand name pharmaceuticals. There are bio-pharmaceuticals and there are generic pharmaceuticals. The typical pharmaceutical industry, and there is no such thing because most of the pharmaceutical companies that I'm aware of are affiliated in some way with a generic, and everything is getting a little bit confusing. But this is -- they develop drugs and market traditional small molecule drugs. And they are expensive to develop and typically easy to copy and cheap to manufacture at scale.

The biotech industry is kind of broadly divided into two areas that develop and produce a biopharmaceutical, biologics, and they include proteins, vaccines, blood products, gene therapies and stem cell therapies. In addition, bioinformatics is becoming very, very important. And these are the gene-based diagnostic testing and pharmaceutical medicines. And they're emerging as very important areas.

The generic industry is also an extremely important contributor to the drug producing area. They take brand-name pharmaceuticals and they make them in the generics. But there are also some new things emerging with respect to biosimilars, which are a little more complicated. Because unlike traditional small molecules, the biologics generally have high molecular complexity and can be sensitive to the difference in the manufacturing processes. So biosimilars manufacturers do not have access to the original manufacturer's molecular clone or cell bank. Nor

do the exact fermentation and purification process. So they're not exactly as easy to manufacture as traditional generics.

Let's talk a little bit about what happens with respect to the development of these drugs. And I'm going to analyze broadly what happens here.

First of all, in the pharmaceutical area there are high fixed costs of product R and D and market entry. Sometimes greater than 1.8 billion per drug. It's a heavily regulated market. There is a long developmental cycle. It's a high risk. One out of every 1,000 candidates identified during drug discovery make it to clinical trial. And these factors make for strong patent protection essential to drug development, essential.

Now, I'm going to say, in my entire career, I have never seen a study that says we should not have patent protection for pharmaceutical drugs, never. And when I hear opining in this area about moving in other directions, I think that before we risk economic development and job creation, we need a little bit more of understanding if there's some other modality that might work and not throw out everything with respect to what we're doing in patents with respect to pharmaceutical.

Biopharma patents are similar. I mean, here we've got different ways, statutory classes for protecting the subject matter. It's product and composition claims. There are method of use claims. There are formulations. There are process claims and there are diagnostic methods which are a subset.

Now, let me say a lot of the cases that have come out recently had what I would call somewhat poorly drafted claims, and that is a different topical issue with respect to those things. And I do think that if we are more creative and thoughtful about where we're really trying to go, we can do a better job in this area without invoking 101.

How is biopharma different? Well, I did a comparison and analysis. Patents in biopharma are significantly more valuable and have a higher rate of return than they do in other industries. In contrast to most industries, biopharma firms primarily use patents to prevent copying of their product. They also rely on patents more heavily as corporate assets. Innocent infringement is very rare. There's almost no patent troll activity. There is an exception to that. There are fewer patents per product. You can see that it usually takes three to eight patents to cover that, where it can be thousands for the high tech industry.

Bottom line, because they enjoy much higher net benefits from patent ownership, biopharma firms generally favor stronger rights and remedies than would be optimal for most other companies.

How is biopharma different? They are discrete versus complex technologies. Higher benefit from patents for products employing discrete technologies that are covered by a small number of patents owned by a single entity. Transaction costs and risk of strategic behavior increase in proportion to the number and dispersal of patent rights.

Patent density. You can take a look at the Orange Book. In patents in nearly -- in 2000, estimated averages between 2.5 and 7 patents per product in biopharma. Compared to more than 730 patent families declared essential for a mobile standard. And despite R and D, IBM spends -- received 7,481 patents in 2014 compared to 128 for Glaxo-Smith-Kline. We have a much higher regulatory environment, and generic competitors cannot enter the market without approval of the FDA, effectively precluding from granting approval of the generic, the incumbent's patent. So there are significant differences.

So what are the major issues with respect to the challenges here? And I contacted the Pharmaceutical Association and the Biotech Association to find out what they thought. And their

biggest issue that they were talking to me about was patent eligibility. So I kind of disagree with some of the speakers yesterday. I don't think that the industry is very happy with some of the decisions the Supreme Court has been making lately.

They also are very concerned about the impact of the AIA, and there are concerns over patent pending bills that are up on the Hill relating to the enhanced pleading requirements, limitations on pre-Markman discovery, mandatory disclosure of patent ownership interests and fee shifting. And their legislative priorities are to obtain biopharmaceutical exemptions from IPRs. I think they're dreaming. Prohibit broadest reasonable interpretation claim construction in IPRs, impose higher evidentiary standards for clear and convincing and invalidly and more liberal amendment of claims in the IPR trials. And I think they'll get that.

Let's specifically talk about some of these recent cases. And that's where you're going to find I disagree with a lot of issues. Mayo. I think that this was one of the most disastrous cases to come out of the Supreme Court related to this subject matter in years. I mean it is terrible. The Supreme Court confused 101 patent eligibility with 102 and 103 anticipation and obviousness. I think that they should have listened to the experts at the Court of Appeals for the Federal Circuit. I think this is a big problem with changing what had been happening in my office for years and years and years of granting diagnostic methods. And I am very concerned with the issues that came out of that.

Lesser so but still a problem is Myriad. Now, I mean you know the facts of Myriad, it was discussed yesterday but you may not know a lot of different issues surrounding it. For example, the United States Patent and Trademark Office, the administration's experts with respect to patent law did not sign the administration's brief. Meaning the patent and trademark experts did not agree with the position of the administration. And it's unheard of not to sign on to an administration brief. So the experts didn't agree.

Then we have the Court of Appeals for the Federal Circuit with technical expertise in the subject matter did not agree. The Supreme Court voted 9-0 unanimous and overturned the Federal Circuit Board. I mean if you're going all the way to the Supreme Court, you kind of have a difference of opinion in some of these areas.

So I think the whole setting for the issue is very unusual. I don't know of any of the Justices on the Supreme Court that have technical expertise. I don't believe their clerks do either, unlike the Court of Appeals for the Federal Circuit.

I think they got the science wrong. I do think an isolated impurified gene or gene sequence is not a compound that occurs in nature. And I even -- I think we're still at rest with respect to CDNA. I don't really see their logic in differentiating there. I think we have a problem.

Alice is directed more toward the software industry or the business method industry. And what the Supreme Court did with Alice is they unified the high tech industry and the biotech and pharmaceutical industry in opposition to the procedures that they've been using, and something that really doesn't happen very frequently at all. So we do have kind of a unified anger at some of these decisions coming out of the Supreme Court.

They in Alice said that they weren't kidding with their earlier decisions, and they were applying it now to issues related to software. They talked about requiring something substantially more. They never defined what it was. They didn't tell the patent and trademark office what test they could use. Nobody kind of clearly understands what substantially more is. So we've got problems.

Just this week we had a very interesting -- while I was here, Ariosa Diagnostics v. Sequenom was denied and granted an En Banc paneling by the Court of Appeals for the Federal

Circuit. Interestingly, I kind of agreed with all three of the sides that the judges argued there. The people who said that they didn't think it should go there, kind of pooh-poohed the decision out of the Supreme Court on *Myriad* and *Prometheus* and the dissent said that the Supreme Court didn't meet it. So I believe that this one will be granted cert.

What here happened was you have a brand-new method for testing for fetal abnormalities, which simply require testing the blood of the mother instead of invasive amniocentesis, which my wife had to do twice. And it is lauded in every medical journal as being revolutionary for neonatal care. And yet they said that because the cells of the fetus were in the mother's cells, it was naturally occurring and therefore should not be granted a patent.

Big problems. And I do think there's a possibility the Supreme Court will make a change there. I'm being told I'm out of time, so I definitely want to move quickly. But like I said, there has to be something significantly different.

With respect to the interparty's review, really, we have one person, Kyle Bass, who is trying to sort stocks by going to companies and saying, you know, I will file an IPR against your patent claim unless you settle with me and pay me a fee. And so there is a little bit of troll activity going on with respect to that.

I do believe the people on the Hill are very interested. Instead of going through the rest of my slides, I'm going to very quickly tell you what I think is going to happen.

I don't agree with the people yesterday. Every organization that I am aware of, and I will specifically say AIPLA, IPO, ABAIB Section, Pharma, Bio, all have in their pockets drafted legislation for changing subject matter eligibility issues on the hill. Nobody really wants to offer it. We're very hopeful that maybe the Supreme Court will see their senses, but the industry, at least from my experience, is very upset with these things. We're risking our economic development and job creation in an area where we really have quite a bit of talent. And I hope that the Supreme Court listens to some of the people who are talking about these issues and understands that this is affecting our community very significantly.

Thank you very much.

[Applause.]

MR. OOI: Good morning, ladies and gentlemen. Jin Ooi with Allen & Overy. And I'll just start by saying we are very proud and honored to be invited to this conference, which has been very, very illuminating.

I just want to talk about second medical use from a UK perspective. And I was thinking an alternative title for this could be teaching an old dog new tricks, the UK perspective. Now, you may recall this diagram or this picture from Professor Russell's presentation yesterday, and I promise I didn't steal it from him. It just seems that we've picked the same picture from the Internet.

Patentability. Some difficulties. So we know that the drug molecule itself is not novel, and there may be no physical change to the pharmaceutical itself required to give effect in new use compared with the old use. Because otherwise, you would be able to claim those physical effects to distinguish the drug for the new and old users such as a different-sized pill or a different formulation.

And also you've heard from Ute and from Judge Meier-Beck that in Europe, the method of treatment of the human or animal body is not allowed in Europe.

So then you've got these two type of claims Ute has briefly touched on. The first one from the EPO decision of *Eisai*, which is use of a substance X for the manufacturing of medicament for the treatment of disease Y, and we call this Swiss form claims. And in 2007, when the EPC patent

convention came in, we've got a new form claim substance X for use in the treatment of disease Y.

So you've got a purpose-limited process claim, which is a Swiss claim, compared to the purpose-limited product claim of the EPC 2000. And for the purposes of double patenting, Swiss claim not directed to same subject matter as the EPC 2000 claim, then it begs the question whether or not the rights in an EPC 2000 claim are broader than a Swiss claim. Does that automatically forward.

Difficulties to the Swiss form claims. In the UK after the decision *Eisai in Wyeth's & Schering's Application*, the court sat unbound and decided that the better view is that Swiss claims are not novel, but given the *Eisai* decision, decided that it was right to construe English statute in conformity.

So the novelty there besides in the new therapeutic use and these are process claims, and that was confirmed in *BSM and Baker Norton*.

Then we go on to 2008 *Actavis and Merck*, where *Eisai* extended to new dosage regimes. And you'll hear from Judge Meier-Beck the *Abbott* decision in 2008.

So the general view is that Swiss form claims are claims to a method of manufacture. And finally, how do you tell whether something is for a particular purpose? How do you tell if the medicament is for this particular use? Suggesting that the "for" might here mean suitable and intended for, and that was the common position adopted by *Hospira and Genentech 2014* by the parties but not argued much further.

So you've now passed through the patentability issues. You've got a second medical use claim. But what exactly is your scope of protection? How far does it protect you from infringement by other generic manufacturers? The way we see it, patent law issues the need for a workable infringement test. And tied in with that are issues of claim construction, what does "for" mean. Direct and indirect infringement. Can you claim -- can you say this infringement under both. Is there actually indirect infringement. And tied into that what remedies are appropriate. But I'll steer clear from that because I know that's the topic for the next presentation.

And then we've got sufficiency and plausibility issues, which is a bit of a hot topic at the moment in the UK where whether or not you have enough data in your patent to justify claiming a broad -- a set of claims. So you've got the cases which have come out very recently in the UK, *Generics and Warner-Lambert or pregabalin and Merck and Verner, ntpB1 antibodies for treating cancer, Actavis and Eli Lilly and Atomoxetine*. A succession of cases by three different patent court judges in the UK talking about this issue. But I won't be going into detail on that.

And then you've got practical issues stemming from the use of skinny labels, which *Jurgen* touched upon yesterday.

So the use of -- the use that can arise where an unpatented use authorized so there are issues of cross-label use and cross-label dispensing, and that's exacerbated by the health care systems which encourage generic prescription and substitution.

Moving on, then, to the UK *Lyrice* case, *Generics and Warner-Lambert*. And before I move on, I should say that the ANS [sic] team and myself are involved in this case for the patentee. So whatever I say here really is in the public domain and publicly and this really represents my views and not that of the patentee.

What is meant by a requirement that medicament be for a therapeutic indication. And this issue is really an important one because it concerns the scope of protection to be afforded for second medical use inventions. And this is the first case where direct infringement turned on ultimate intended use. And two questions could arise from that. Whose intention is it, which is

relevant, and what's comprised in the requirement of an invention. And I'll touch on these two questions later.

So let me then turn to the facts of Generics and Warner-Lambert. You've got a drug, amoxin by Warner-Lambert, who's part of the Pfizer Group, which is indicated for three indications, epilepsy, generalized anxiety disorder and pain. Warner-Lambert is the holder of a patent for the use of pain, the compound patent having expired -- have expired quite some time ago. The dosage forms and recommended dosages are the same for all three types of indications.

You've got a situation in the UK where doctors write the prescriptions generically or by I and N. So you'll say pregabalin. It wouldn't say the drug Lyrica or the other generic manufacturers' drug names. And you've got a situation where the indication of the particular drug isn't mentioned in prescriptions. And so you would expect generic manufacturers who did, and they did carve out skinny labels from their marketing authorization to market their products for epilepsy and generalized anxiety disorder and saying that the indications for pain are not aimed at or targeted for.

You have got a situation in the UK National Health Service where you've got devolved nations in each of which autonomous bodies. And in England alone, you've got 210 clinical commissioning groups and multiple health boards of Scotland, Wales and Northern Ireland each of which is an autonomous body.

So you've got a situation of thinking where, then, do you stop a generic product being marketed for pain? Do you go -- is the solution residing with the department of health with NHS England, with any of the devolved nations, or is the solution with the CCG for the health boards. Of course in one side you've got the people in the left, which are your -- your left, which are Pfizer's clients, and you've got generic manufacturers who obviously are selling the drug for generalized anxiety disorder and epilepsy.

And just a quick word under reimbursement and drug tariff, as I said, doctors are encouraged by higher ups to prescribe generically. And when that prescription comes to a pharmacist, that's obviously not written for an indication. Judgment says that most of the time pharmacists won't know what indication pregabalin is being prescribed for and obviously get incentivized to dispense the cheaper generic product because the level of reimbursement for pregabalin at least and still is at this stage, are the same. So really, if you dispense a cheaper drug, you get a larger reimbursement fee.

So you've got a situation where you've got a second medical use patent. You've got generics, sort of a marketing authorization. We see a label carving out the patented indications. And they don't advertise beyond their marketing authorization. You've got doctors prescribing generically and prescription software, which encourages them to prescribe generically.

You've got situations where generic product may be sold for the patents and indication. Pharmacists incentivized to dispense generic products, who don't know indication and are further encouraged by the drug reimbursement tariff. And the question is this: Does that fact pattern, then, amount to infringement? Is there infringement by generic companies of a Warner-Lambert patent?

Very early on in the case following a refusal of interim relief -- and I won't touch on that because again, that's next topic on relief -- there was an order to NHS England to give guidance to the NHS service providers, which says medical practitioners should prescribe only by brand name Lyrica for the patented indications, that pharmacists should really dispense branded products when they are told or when they know it was for the patented indication and to consider amending prescription software so that if it's prescribed for pain, that you should prescribe by the brand name Lyrica.

And quickly for the reasoning behind this guidance, it's because NHS England was best placed at -- it will be consistent nationwide guidance, which has the force of encouraging the CCGs, GPs to describe and dispense in the manner as mentioned. And the judge also said that the best solution to a problem of second medical use patents is really to ensure that doctors prescribe by brand name rather than generic name.

So then moving on to the test for direct infringement, what does "for" mean? In the higher court in interim injunction stage, the judge says it was subjective intention. What the generics are thinking of when they're selling their drug for the nonpatented indications. Then it went on to the Court of Appeal who then said well, the test really is whether or not the generics know or foresee reasonably that their product will be used intentionally for the treatment of the patented indication. And when that test was applied in the facts of September of this year, the judge referred to intentional use to be that for the generic-specific product and requisite intention was that of a doctor or pharmacist, not the patient.

So you have a situation here where the doctors are prescribing generically. They don't say -- doctors don't intend Actavis's product Lucian, being prescribed for pain. And you've got a situation where the pharmacists don't know an indication for the prescribed drug. Well, that's a result that the judge said there's no foreseeability that Actavis's specific product will be intentionally administered for the patent indication. This is all obviously still pending appeal.

And just I note there the fact the NHS guidance obviously makes the use of the patented indication less foreseeable when you've got a situation where doctors and pharmacists are encouraged to prescribe the Lyrica drug for the patented indication. But then it's a question of how effective the guidance has been in the UK, and that's now a matter for debate.

Moving, then, on indirect and contributory infringement. There's a need under the EPC 2000 and the UK laws for a downstream event which could be regarded as putting invention into effect. So this would mean for Swiss Pharma claims, because the pharmacists don't use Lucian, Actavis's product, to manufacture the pharmaceutical composition because it has already been received -- it's been already manufactured when they receive it. So then looking I guess what you were saying as well to the literal construction of a Swiss form claim or do you read it purposefully.

The Court of Appeal allowed the indirect infringement claim to go on to be heard at trial. And that trial, it was held that there wasn't any contributing infringement. The infringing fact was the manufacture and there was no downstream act of manufacture. I said here that the Court of Appeal was encouraged by some of the European cases. In Germany, Hacksell and Elliott [sic] case and Warner-Lambert, which you briefly touched on. And Novartis and Sun, which had a court of appeal judgment, just another court of appeal judgment coming down last week, which I'm sure we will be discussing in the next session.

So then some key policy issues. Collision with the health services' approach to cost savings. Is there any obligation of either party to act ahead in time of loss of exclusivity to partition the market? So you've got drugs for patented and nonpatented indication. Is it fair to find infringement when reasonable steps have been taken when a generic company says they've written dear pharmacist letters to pharmacists saying that you shouldn't be dispensing our generic product for the patented indication. And in circumstances where they've taken steps to carve out the patented indication from the marketing authorization.

Some unanswered questions. What should the legal test be? Is it a once and for all test or is it something that can be looked at again and again? Obviously intention changes and knowledge changes. Can contributory infringement apply? What does this mean by putting invention into effect? What final remedies are appropriate? What solutions are available in more complex cases

where you've got drugs in a hospital setting and home care products? Do the EPC 2000 claims make any difference?

So I won't touch on any of these, but I'm more than welcome to discuss this during Q and A session or at the break.

And then finally my last slide and position is Australia, because that's where I started my practice in. You have a situation where it's very similar in the U.S. where method of medical treatment of human body is capable of being patented. So you've got a method of treatment claim, compound when used claim, Swiss-style claims often drafted into saying patents because -- on the basis they may have different scopes.

This has been finally confirmed by the highest court in Australia in 2013 Apotex versus Sanofi-Aventis that you can actually patent -- a method of medical treatment is allowable. In that case, you've got again a skinny label for leflunomide, where the generic has carved out the patented indication. And the test there for indirect infringement is whether or not a generic has a reason to believe that their product will be marketed for the patented indications. And in that case, it was held that there was no reason for Apotex to so believe.

But again, the marketed side of patented and nonpatented indications is important especially in Warner-Lambert, Apotex, where the patented indication accounted for over 95 -- 99 percent of the patented indication. So in circumstances where Apotex tried to sell their product for the nonpatented indication, there was clearly reason to believe that they would be selling for the patented application.

And that's the end of my presentation.

[Applause.]

HONORABLE MEIER-BECK: Good morning, everybody. Thank you, Toshiko for inviting me to contribute to the great event. It's a pleasure to be back to Seattle.

The Supreme Court judge should be cautious and should say nothing what is not an incontestable truth or has already been decided by his court and is therefore an uncontestable truth.

MR. STOLL: Another joke.

HONORABLE MEIER-BECK: Sorry. I'm a German judge. I am a bit confused to hear that the same is not true in the United States, but anyway. This is my table of content with incontestable truth.

An invention shall be considered to be new if it doesn't form part of the state of the art. And the state of the art shall be held to comprise everything made available to the public before priority date or application date. You may be familiar with that. But the reason why I mentioned it is the consequence of this principle of novelty, is that novelty requires a new technical teaching. And that is decisive for many questions we discuss today when it comes to patentability and when it comes to infringement. Because a discovery as such does not establish a new technical teaching and is therefore, as such, not patentable. Although the same is explicitly said in the statute. But if you hadn't this provision in the statute, the same were true because a discovery as such does not contain the technical teaching, but something that exists in the nature.

And nevertheless, an invention in the new technical teaching may be based on the discovery especially on the discovery of a natural biological mechanism. And according to European and German law, and contrary to what has been decided by the U.S. Supreme Court for the United States, when assessing inventive step, the discovery should not and must not be disregarded because it is not patent-eligible itself, but nevertheless it may be the only -- the main and the only inventive contribution to the new technical teaching and may therefore be sufficient for granting patent protection.

In the Memantine case, that was these two elements: That the discovery is sufficient as long as a new technical teaching results from this discovery. Where the basis of the decision we made, it was about a substance for the treatment of Alzheimer's disease. We heard about a substance for treatment of Alzheimer's disease yesterday afternoon.

The basis of the patent was the discovery of the function of an active agent which served as an antagonist against a specific pathologic status linked to Alzheimer's disease. But it was a very valuable discovery to describe this function of this agent. But unfortunately, there was no new technical teaching following from this valuable discovery because neither a new dosage regime was taught nor a group of patients so far not treated with the agent was disclosed to be a responsive group. So therefore, the patent was invalidated in the location proceedings before my court.

I mentioned Article 54(2) EPC, which states that the state of the art shall be held to comprise everything made available to the public by means of a written or oral description before priority date or filing date. But we have, as you know, Article 54(4) EPC that states that that provision shall not exclude the patentability of any substance or composition comprised in the state of the art, for use in a method referred to in Article 43(c) that is for the message for medical -- of medical treatment. And we have in the EPC 2000 mentioned by Ute Kilger in her presentation.

Article 44(5) that states that patent protection may be granted for any specific use in that message referred to in article 43(c). So for any specific use for medical treatment or surgery.

As already mentioned, the enlarged Board of Appeal decided in 2010 that, where it is already known to use a medicament to treat an illness, Article 44(5) does preclude that this medicament be patented for use in a different treatment by therapy of the same illness. But such patenting is also not excluded where a dosage regime is the only feature claimed which was not known in prior art.

This decision has been approved by my court in a judgment given in 2014. And in the claim, there was an interesting feature in addition to a dosage regime. You see on my slide the claim. The claim states the disease that has to be treated by the substance. There is a dosage, conventional dosage regime -- scheme given in the claim and there is an additional feature, and the most interesting feature of this case and it's the last one. The claim says that the hand with fibrous cord has to be immobilized immediately after injection of the substance and maintained to be immobile for several hours.

And the Federal Patent Court that has to deal with this claim, the court first instance invocation proceedings ruled that when assessing inventive step, the last feature has not to be taken into account because it did not relate to the substance or the dosage scheme but to the method of treatment, the method how to treat the patient when administering the substance. And because the remaining elements of the claim were obvious to a skilled person, the patent had been revoked.

When we had to deal with the appeal, we -- first we made clear the following: As a matter of principle, it doesn't -- it doesn't matter for patentability issues whether you have an EPC 2000 claim, whether you have a use claim, German-type use claim as Ute mentioned, use of X for treatment of Y, or if you have a Swiss-type claim as granted by the European Patent Office, which, as you may be aware of, did -- does not grant these German-type use claims. Because the enlarged Board of Appeal thought that it might be impossible to grant claims for the use of a nonmedicament for different purpose.

We thought that's unnecessary. But anyway, at the very end, it's all about purpose-bound, purpose-limited substance protection. That is the essence of the EPC 2000 claim that is the essence of German-style use claim and that is the essence of a Swiss-type and use claim.

We approved the general approach of the enlarged Board of Appeal in Apotex, and we added that the specific use of a substance may be determined not only by the disease to be treated and the dosage scheme, but also by other parameters that influence the effect of the applied substance.

Or to put it differently, may be of critical importance for the entry of desired success of the substance-specific use. But that does not mean that anything which relates to the treatment of the patient in combination with such administration, with administering the substance concerned can contribute to the new technical teaching therapy-related instruction can only do this if they objectively target allowing, amplifying, accelerating on any other way improving the effects of the substance but not so relate to a therapeutic measures which in addition to an independent of the effects of the substance are suitable to treat the disease in question.

I think time is over and so is my presentation. To foster pharmaceutical innovation, that's my conclusion. Any specific use of a substance for therapeutic treatment is patentable if the specific use is new and involves a new inventive step. The letter is important. It's true that patent protection for second medical use is a valuable incentive for developing new use of existing known drugs. And so second medical use patents are valuable contributions for -- to allow us to reach sufficient protection of innovation. But on the other hand, we have to be aware that this tool itself is an incentive for inventive -- for inventing advantages of slightly changed dosage schemes, for instance.

So we have to balance both aspects. Second medical use patents are important but we have to -- we have carefully, we have to consider carefully in each and any case inventive step. Same is true for the patent I have talked about, and we couldn't examine the inventive step because it wasn't appealed on precedent of law only, so we have to send the case back for the Federal Patent Court for considering again inventive step in the case at hand.

In any case, courts have to ensure the appropriate balance between patent protection and freedom to operate and to use an existing substance, known substances for known treatment methods and for known purposes. And at least this I think is an incontestable truth.

Thank you very much.

[Applause.]

MR. SERAFINI: Thank you, Professor Meier-Beck.

So before we open up the floor to questions from all of you, I have a few questions for each of our panelists to get the discussion going. And in this case last is first so as you just sat down, Professor Meier-Beck. I have a question for you: Noting all the caveats that you used when you started your presentation, and we'll ignore the joke or the absence of a joke that you may have made. So if you'd accept the premise that the EPO -- and this is personally my belief, that EPO is now one of the patentee and in this case innovative drug-friendly legal frameworks, and that the G208-case that you spoke about, the dosage regime Abbott case, provides a fantastic opportunity to pursue creative second medical use claims in Europe.

How far do you think the regime Abbott case -- the dosage regime Abbott case can be taken?

HONORABLE MEIER-BECK: Yes, I think it's -- when this decision -- when the EPO came up with this decision, I was a bit skeptical at the very beginning that this approach may be a bit too broad and give too much particularity to grant patent protection essentially for medical treatment. But I think as we recognized in our judgment, there is no grasp -- agenda to grasp how to deal with second medical use in a narrow but similarly clear -- and clear way. So I think it's -- if it's applied carefully, I think it's -- it ensures a good balance between patent protection for second

medical use and avoiding evergreening patents on the other hand, which is also an important goal of our -- of applying this tool of granting protection for second medical use. But that shouldn't be the result of evergreening patents with slightly different shaded dosage regimes. And we should always be aware that for a patent examiner it may be quite difficult to find out what it's really a novelty of when he's confronted with more or less clear evidence on the advantages of a different dosage scheme, for instance.

MR. SERAFINI: Thank you, Jin, until recently you had two specialists in the High Court, two specialist patent judges, and I think now I believe you have three, Arnold, Bears and Carr [sic], which both of them seemingly applied different approaches.

And as more of a side note, I think there have been similar cases recently reached where a decision opposite in the Netherlands court. Do you think -- and we hear a lot in the United States a lot about the Unified Patent Court. Do you think the Unified Patent Court will solve these differences and the different views especially now that you have three High Court patent judges added to the mix?

MR. OOI: I mean I think that's the hope that EPC would come up with some sort of a unified solution. But I think the reality is, in my view, it's going to be really dependent on the sort of panel of judges that you're going to get in EPC. Because you're going to be bringing from your background, the English system or the German system or the Netherlands system. And to the extent possible, I guess they'll sort of come up with a unified approach and that may be the solution as the EPC continues on many, many years down. But I think in its nascent stages, anyway, I think there will still be possibly differences.

MR. SERAFINI: Thank you, Jin. Bob, you're often shy to express your opinion, so I'm going to ask you to kind of stretch a little bit and maybe come out of your shell. And if you need to take a moment, that's okay too.

You addressed in your talk, this legislation by all these different groups related to the patent subject matter eligibility. What is your personal or if you wish your professional view on the prospects for this legislation going forward?

MR. STOLL: That's a tough question to answer. I don't -- I don't think that any of the groups right now are ready to introduce any type of legislative fix at this point. Because once that happens in Washington, D.C., you lose control and there is a possibility of things running amok with respect to the proposals at that point. So I think that most of the -- I am on at least one, possibly two of those task forces, and we do have legislation that's ready to go in case somebody introduces something we really think is very onerous, but we don't want to do it.

We're hopeful that the Supreme Court will revisit some of these issues and that the pendulum will begin to swing back a little bit. We have from the biopharma area, the areas case. In the high tech there is Planet Blue, which also has the technology of matching the movement of a character to speech which was denied patentability based on 101 utility.

But I'm beginning to think that the court is tiring of 101, which was supposed to be a broad filter. I think that what needs to happen now and what I'm advising my clients is to have better defined boundaries of their claims so that people clearly understand what they're claiming, meet their obligations under 112 with respect to clarity, written description enablement, and that's where we should really focus our attention instead of 101.

Knock things out with prior art. I have no problems with using 112, 102 or 103. I just believe 101 should be a very broad filter that then allows for other things to happen with other pieces of the statute.

I would also at this point, I'm telling my clients, to take whatever the claim that the patent office is willing to grant and then file a continuing application on the other claims that are maybe violative of the current rules, but I think that eventually things will change, and you need to have something in the hopper to be able to claim it eventually. So I'm saying bulk up your specifications, be clear on your claims, draft them thoughtfully, and in due course in time, we may see the pendulum swing back, particularly when all of our biotech and pharmaceutical industry moves to Europe.

MR. SERAFINI: We have to keep in mind that Myriad and patent eligibility is not such an issue in Europe, so I think you've seen some leakage in Australia.

MR. STOLL: Yeah, they seem to follow our Supreme Court on Myriad. However, the lower court actually slapped Myriad down, correct? So they have the same problem we have.

MR. SERAFINI: Well, thank you, Bob, for being shy.

Two more questions for our panelists, and then we can open up the floor to questions from all of you.

Ute, briefly, can you explain in a little bit more detail what you mean by inherency, the inherency doctrine? I personally don't understand how, you know, that would make a claim novel if the novel patient group treated overlaps with the patient group treated in the prior art. I don't understand that.

DR. KILGER: So essentially, I think it is the view of the patent office is if something is hidden in the nature or somewhere and you have not provided as technical teaching to the public, then it's not there. So and I think in most situations, the European Patent Office will not view a medical treatment that occurs inherently in the prior art as being publicly disclosed. So -- and I think that this is quite a good approach because it encourages like personalized medicine, so it encourages that you really look for responders and markers and that you stratify the patients and only treat those who respond.

There were earlier decisions of the European Patent Offices where it was the T200 in 1996 where they introduced a two-part test and they said this patient group should not overlap. But all the recent decisions are they took this away and they stated there is no inherent treatment if you have not known that this patient group is a responder, this is novel technical teachings. And in fact, you really change the way the medical practitioner is now acting. And this leads from a discovery I think to an invention.

So everything is nature and everything is maybe a discovery. But then you turn it into a technical teaching and that makes all about the difference. **MR. SERAFINI:** Great. Thank you, Ute. And finally, Shinjiro, is there any disadvantage for the coming new practices of PTE with the Supreme Court decision in Japan in November?

MR. ONO: Yes. The point is I think that I explained. There used to be GP consider that I think the extension and the scope of extension and their approval. I think this new Supreme Court decision said that the same IP High Court decision is I think every time and the prior approval and comparing it with I think the subject new approval, and if they are identical, I think there are no distinction.

But if there I think the second approval is not identical, it's a different from the first one from the authority, it is possible to extend. That means it used to be GPU consider the extension of I think scope of the extension is I think very broad. Because it's in the claim scope, but I think this new decision implicate that the scope of the claim, scope of protection is very narrow, only limited to I think shall we say the approval. That is very narrow one.

Therefore, I think the user or a company should be very careful about if they apply for the new extension but also they consider for the R and D. Two, I think they apply for the new extension as long as because of the scope of the extension is very narrow comparing with the old style, that is I think a little bit cumbersome for the company to be careful about and for protection of the scope. It's very narrow. That is I think one of the...

MR. SERAFINI: Thank you very much. I know you're all very eager to come up to that microphone or that microphone over there and ask -- assault our panel with questions, so we encourage you to do that now.

And the first to the microphone is the first question that will be asked, so that's over here.

AUDIENCE MEMBER: I am a European patent attorney and I have the same problem as Andrew actually understanding how this EPO case law regarding patient subgroups, especially when it comes to the overlapping patients. I would have assumed, okay, if you have a patient and then you make the discovery that the reason why he was treated was because he had this gene marker, that should not be even novel at least with respect to that. And I see a difference with the Memantine decision where they clearly say it has been previously untreated. I know you hate to make predictions for the future.

Peter, but when you look at this case, how would you have decided?

HONORABLE MEIER-BECK: I refuse to answer this question. But I agree with you that there's a difference between the Memantine decision, and this approach that is a discovery of why patients have been well treated by administering certain substance sufficient to constitute novelty.

MR. SERAFINI: Question?

AUDIENCE MEMBER: Yes. This is a question for Mr. Stoll as he's been a little shy here. I'm going to try to draw him out here a little bit. In all seriousness, I appreciate your candor very much. You spoke about U.S. legislation and I had a follow-up to that. You -- earlier in your comments, you touched on Kyle Bass and what he's doing in the industry. I'm wondering what your perspective is on any Big Pharma introducing any sort of legislation either in this year or next that would fix or address the kind of activity, shenanigans that Mr. Bass and his cohorts are up to in their approach to leverage the IPR process.

MR. STOLL: That's a thoughtful question, and it depends on what type of legislation you're talking about. Firstly, though, I will say I don't think anything is moving at this point right now. I would say that, you know -- and we've got an election year next year, which means things are going to take time. I do believe there was an attempt to take him to court on RICO charges in New Jersey at one point, which I thought was very interesting. And I think some of the things I've got a little bit of problems when he goes privately to the company and brings that IPR already drafted to them and hands it to them. I think that is a mistake in my opinion as to what he -- but the rest of it I think is probably within the boundaries of the law.

I do think he can, as a concerned individual so to speak, bring an IPR. And I don't think there's any limitations. But that was specifically contemplated in developing the IPR in the AIA. I think based upon what he's doing with it, we now need to rethink that, whether someone has to have an interest or not. And I think I believe in full debate and discussion because I don't like what he's doing. But I do think that there are some public interest groups who might have an interest in removing what I call dead wood from the IPR system.

I also believe that we need more ability to amend the claims, which is why you have the broadest reasonable interpretation in the first place. And the PTO hasn't been able to do that, which could take some of these problems out of the system. There may be some tie to things that have

already got FDA approval or, you know, are farther down the pike. And there may be ways to draft legislation to kind of exclude those types of things. But I think it's going to be difficult to do because of -- because of all the other competing interests.

So I share your concern. I don't like what he's doing. You know, I think it smells to me. But I think that most of what he's doing is completely legitimate, and I hope we're able to find a way to stop that. And, you know, getting a better quality patent out of the trademark -- patent and trademark office goes a long way to reducing the number of IPRs that are filed. So IPR can only be brought on prior art, and if we do a better job taking care of the prior art making sure that it's in front of the examiner and they understand it and they're only issuing patents, at least to a larger degree, that are completely valid, we remove the Kyle Bass problem itself.

So there are many ways to tackle this. Sorry for the long answer.

AUDIENCE MEMBER: Thank you very much. Just so I understand your comments fully, next year election year here in the U.S. so probably nothing.

MR. STOLL: Probably not.

AUDIENCE MEMBER: This year.

MR. STOLL: Probably not. That's my answer.

MR. SERAFINI: He just put new batteries in his crystal ball. So, Toshiko, do you have a question?

PROFESSOR TAKENAKA: Yes. I'm completely with Mr. Stoll and I am very concerned about sort of activism. The Supreme Court here in the United States as well as Japan, because the activities isolate Japan or United States from the rest of the world. This has sort of, you know, undermining force done by U.S. PTO or JPO. So therefore, I'm also concerned about the new sort of Unified Patent Court, which will be also be enacted maybe isolating or undermining harmonization activities.

So I want to hear from European speakers about what sort of impact a unified court will have as well as what sort of the things U.S. PTO or JPO can do to prevent sort of -- prevent undermining the activities for harmonization.

MR. SERAFINI: Ladies first, Ute, or Jin.

MR. OOI: I mean I think my answer is going to be quite similar to the one I gave previously. What we're saying now that UPC is really going to be crystal ball gazing. We're really going to be hoping that some sort of unified approach is going to come up. But with the opt-out/opt-in, you're still going to get national decisions on patents, and it's going to be a very, very long way in my opinion before anything consistent will resolve. But I'm interested to hear.

DR. KILGER: So I totally agree to this. First of all, I do not think that all the users will put all the balls into the system and to see what happens with their most precious IP. So it may take a while that the system is going to be tackled and it may take a while that it is consistent and harmonized, but it's really a crystal ball, as you said.

MR. STOLL: And with respect to what the U.S. PTO can do in the cases that are coming down, if you read them very carefully, they're very narrowly decided, extremely narrowly. And what the U.S. PTO can do is interpret them very narrowly in their implication and their guidelines. And they have been good about making iterative changes. I am still asking for more. I think they need to be narrower. There's many things I think can be done.

HONORABLE MEIER-BECK: I do think it's hard to predict what will happen when the UPC Pharma will start working and the court will have to find its way between the established EPO case law and the -- in one different national and jurisprudence. And I -- personally I hope that there will be judges who are experienced enough to find their own European way to a certain extent

independent to what is now established practice of the EPO. But everything will depend especially on the judges of the Court of Appeal.

MR. SERAFINI: Great. Thank you. One last question and we're cutting to our coffee break.

MR. FEHLNER: Paul Fehlner from Novartis again. What role do the patent offices have to play in helping craft the claims that will stand up to further review downstream and that will be meaningful from the perspective of actually supplying that reward for innovation that we discuss the patent is intended to supply?

MR. STOLL: I think the patent offices can provide guidance as to what type of claims are going to pass patent-eligibility muster. I think they're starting to do that. I see a lot of examples being put forward out there which I think is very helpful. I would recommend also, I mean I hate to admit this, but I see allowability rates vary from art unit to art unit. I do some of these tools and formulate my claims in a manner that would put them in the art units that have a higher allowance rate.

So I -- technically, I use a patent advisor myself, and I also try to route my claims through systems that make sure that there is quote/unquote substantially more so that we move forward. But I keep something pending, you know, if I get an allowance I take it, and I do a continuation because I do think things will change.

MR. SERAFINI: All right. In closing, I know that I opened up the session joking about the gray skies. As you can see there is sunshine outside. In the Pacific Northwest, they refer to that as a sun break, and the moisture that falls from the sky is also referred to as liquid sunshine. I'd like to take this opportunity to thank our esteemed panelists for their participation. And let's give them all a great round of applause.

[Applause.]

[Recess was taken.]

PANEL V
REMEDIES FOR INFRINGEMENT OF NEW USE DRUG PATENTS

Moderator:

David Tellekson, *Fenwick & West (Seattle, WA, USA)*.

Panelists:

Simon Cohen, *Taylor Wessing (London, UK)*.

Hon. Rian Kalden, *Dutch Court of Appeal (The Hague, Netherlands)*.

Dr. Matthias Zigann, *Munich District Court (Munich, Germany)*.

Hon. Toshiaki Imura (ret.), *Yuasa and Hara (Tokyo, Japan)*.

Hon. Garrett Brown (ret.), *Chief Judge, U.S. District Court (D. NJ) (ret.) (New York, NY, USA)*.

PROFESSOR TAKENAKA: We have special guest, meaning Dean of the law school. She was supposed to be out of town but very fortunately that commitment was canceled so here she is, Dean Kellye Testy.

DEAN TESTY: Thank you so much, Professor Takenaka. I wanted to take a very quick moment as this panel begins to tell you how pleased we are that you're here at the University of Washington School of Law and in William H. Gates Hall. I know from what I've been hearing from my colleagues and from some of you I've talked to in the hallway that things are going great with this event. And I just wanted a chance to tell you how much we're welcoming you all here and how much we're pleased we'll be able to be a part of this.

I also wanted to take just a brief opportunity to thank Sir Robin Jacob, who is of course leader of this event, and it's been wonderful to be able to get to know him and work together on this. And then I also wanted to give a great thanks to two of my colleagues. I want to thank Mr. Terry Price, who's been a key organizer. And then especially thank Professor Toshiko Takenaka, who is one of the world's leaders in patent law and a colleague that we're just so pleased to have here at the University of Washington School of Law.

So Toshiko, it's wonderful to see you here and I thank you for your leadership. And again thank you for giving me a minute to say hello, and I'll not stand in the way of progress any longer and turn it over to this panel. So again, enjoy. Thank you.

[Applause.]

MR. TELLEKSON: I'm David Tellekson of Fenwick & West, and we have a very distinguished Panel 5 to talk about infringement of the new use drug patents and also remedies for that infringement. And let me just introduce briefly the panel and then we'll get started.

We have the Honorable Matthias Zigann of the Munich District Court. And next to him is the Honorable Rian Kalden of the Dutch Court of Appeals. A nonjudge, we have Simon Cohen -- well, he's currently missing, but he'll be here momentarily. And also the Honorable Toshiaki Imura, who is a retired former Chief Judge of the Intellectual Property High Court in Japan now with Yuasa and Hara. And the Honorable Garrett Brown, who is the former Chief Judge of the Federal District Court in New Jersey, is now retired.

So very distinguished panel. And the Honorable Judge Zigann will start off.

MR. ZIGANN: Good morning, everybody. And my special thanks go to Toshiko for inviting me over. I really appreciate being here. And just for the record, it's Matthias Zigann.

We decided upon giving me some more time to present what I have to say, as I will show you through the pregabalin case, as it happened in Germany. And as you will learn from our following speakers, it also ran in the Netherlands. And you have already heard that it ran also in Great Britain and Australia.

And the methods I would like to use is kind of different to the methods you have seen by the previous speakers. So I would like to give you an outline of the facts of the case and then we go a step back to the law as we have it in Germany. And then we will look at the decision of the Hamburg Regional Court.

So the facts are that we have two medicines in the market, the one medicine labeled for epilepsy, generalized anxiety disorder and neuropathic pain. And the generic one labeled for the same but not for pain, so it's kind of skinny labeling. And then we have the patent, a European patent drafted according to the Swiss Patent Office so-called Swiss-type claim, which reads, use of pregabalin for the preparation of a pharmaceutical composition for treating pain.

And what happened, the doctor prescribes pregabalin with no indication to the brand name usually. The pharmacist receives the prescription and by law, is obliged to hand over the most inexpensive one. To do that, we have software in most pharmacies pointing out the cheapest drug containing pregabalin. And in addition to that, the law provides for the health insurers to be able to get into rebate agreements with pharmaceutical companies.

So in our case, as decided in Hamburg, the defendant signed a rebate agreement with the health insurer called KKH about pregabalin. What they did not do was to sort of carve out the second medical use for treating pain. The rebate agreement is silent on treating pain.

So plaintiff argues, given the regulatory environment in Germany, just by producing the drug and by signing the rebate agreement, you are infringing my second medical use patent. Because it's sure that because of the preconditions, your drug will be used to treat pain. Also the label of your drug does not indicate it to be used to treat pain.

I have some difficulty with my eyesight as this is not the right distance for my glasses. I have to refer to the other ones, to the printouts.

So looking at the law as we have it in Germany, we have at Section 9 of the German Patent Act covering direct infringement, this is quite lengthy. I broke it down to the essentials. So we have product claims and process claims. And as you can see, specific activities are exclusively reserved for the patent owner. And if you look the process it's using and offering to use, and if we have a product produced directly by process, it's offering put into the market and so, on as you might know from your own jurisdiction.

Now, as discussed before, if you look at the Swiss-type claim, we have use in the manufacture of a medicament for the treatment. That's basically a process claim. We use something in doing something. But we also have before for the treatment, and this indicates some kind of purpose.

And going back a little from the slide you see at the moment, the basic problem as I see it is that our lawgiver, our Parliament is kind of inactive with this problem.

So we have now the law that the second medical use can be patented, but we don't have a specific law what happens then. So we have the basic law for the time before this was the case and somehow the judges, the courts are in the duty now to find practical solutions as to have a balanced approach, patent protection for second medical use patents and freedom to operate for the generic companies.

The approach at hand as the German courts saw it, was not to stick too much to the wording of the claim, but to look where is the invention and what is a practical approach when we look to infringement.

And they came up with the *sinnfallige Herrichtung* in German, manifest or purposeful arrangement, as you have heard before this morning.

The effect of the theory is to be able not to look at the use for the treatment, but more have to focus on the manufacturing process, which means that you can sue the generic company for manifest purposeful arrangement of the drug in the first place, which is a direct infringement versus suing then for indirect infringement. Because of course the generic company is not curing anybody, they are producing the drug. Other people are using to cure the disease.

So what could be the manifest arrangement. It could be confectioning, a ready-to-use preparation, dosage and in addition to that, also not concerning the drug itself, it could be label instructions.

Directly infringing acts under this theory would be manifestly arranging for the patent and use and often putting to the market and so on products that had been manifestly arranged.

Not directly infringing acts, according to the jurisprudence of our courts, had been making the drug as such or for not patented indication. And in addition to that, acts not sufficiently attributable to the product, which we see on the next slide. And these cases were decided in Dusseldorf by the first and second instance court, and we had general announcements and marketing materials, flyers, indications by salespeople and so on. And they were not deemed to be direct infringing acts, as these acts were not sufficiently attributable to the product itself.

The specialty about these cases is that plaintiff had been asked by the Court whether or not they wanted to plead for indirect infringement as well. And they answered no, we don't want to do that. So these decisions don't say anything about indirect infringement.

Now, with the EPC 2000, we sort of have a product claim at the moment, X for the treatment of indication Y. Do we have any reason to grant a different or broader scope of protection to these kind of claims, and is the concept of manifest arrangement still applicable? I don't know. We don't have any case law. And so it's entered into force in 2007. Maybe not. Maybe you remember what Professor Meier-Beck just said, that, when looking at the question of patentability, all these different kinds of claims we have at the moment, the German type of claim, the Swiss-type of claim and the EPC 2000 type of claim, in his opinion are the same approach to the same problem.

And the invention lies in a second medical use. That's the invention which should be protected, disregarded the concrete wording of the claim. And also I know that it's the principle in German law that the claim is the name of the game.

We sort of have a very peculiar special situation, as pointed out before, as the Parliament didn't give us any clue how to solve the infringement problem of these kinds of claims. So I think the courts are free or have at least some more freedom to search for appropriate solutions.

Now, let's have a look at the indirect infringement law. It's again very complicated, so I broke it down to the essentials. What is reserved for the patent owner is offering or supplying so it's essential to know that the protection itself can't be enjoined.

Offering or supplying means relating to an essential element of the invention for use of the invention if said third party knows or it is obvious from the circumstances that such means are suitable and intended for use of the invention.

According to the case law we have, this would mean in our case offering or supplying a drug suitable for the patented indication for manifestly arranging within Germany for the patented

indication if the person offering or supplying knows that the drug is suitable and that the custom intends to manifestly arrange the drug for the patented indication.

So it all comes down to the manifest arrangement. And anything going downstream, which is not manifestly arranging the drug but just administering it, would not be a direct infringement. In addition to these two laws, direct and indirect infringement, we also have the principles and secondary participants to patent infringement. But they all need intent. And you have to prove as a plaintiff, the intent of the defendant.

I think that all the jurisdictions kind of have the same principles in this regard, which what may be peculiar to German law would be the law to the principles as a principle is any person who commits the offense himself and/or through another. To commit the offense through another person, the other person doesn't need to have intent. And it's kind of the marionette of the person acting.

Now, let's have a quick look at the remedies at hand because it's quite a difference. So if you can show direct infringement, you may have an injunction on all the acts reserved to the patent owner. If the court only finds indirect infringement, the injunction only goes to offering or supplying the drug without informing the customer that he must not manifestly arrange and so on, which of course is kind of a labeling, which is best use to use the drug which is offered or supplied.

Who are the possible defendants in our case? You of course can go for the generic manufacturer, the salespersons, the pharmacist, the health insurer, the software supplier, the doctor, but not for the patient. Regarding pharmacist and doctor we have one exclusion of the patent law if it's an individual prescription for single preparation of a drug by the pharmacist. But just writing out a prescription for such falls not under the exclusion.

So now let's get back to the decision of the Hamburg Regional Court. It's a PI proceeding. And what they said was they don't believe anymore in the concept of manifest arrangement, which is kind of revolutionary for us in the German law. Nevertheless, they did the test of manifest arrangement and found that the preparation of the drug under the rebate agreement is enough to fulfill the test of manifest arrangement. And the only thing left over was the intent for the use to treat pain. And this intent is confirmed by signing the rebate agreement as the pharmacist is bound by the social laws in Germany to provide the cheapest drug, which is the drug by the generic company. And therefore, the injunctive relief was granted.

The Court said carving out skinny labeling does not exclude indirect patent infringement if the rebate agreement is not limited to the nonpatented indications. And the obligation under social law in Germany to not dispense or substitute -- or justify -- social law to dispense or substitute does not justify an infringement of the patent. Patent law must be met at all times. And that's a nice principle we have in the German jurisdiction or nonunity of the law.

Maybe it's of interest what the operational part of the judgment was in detail. So Hexal, the defendant, must not enter into a rebate agreement on pregabalin or supply Pregabalin in course of such a rebate agreement if the use of Pregabalin for treating pain is not excluded and so on. So this is the injunctive relief they got.

The decision is silent on damages, as you can't sue for damages in PI proceedings. But this would be a very interesting point of law how exactly do you calculate damages in such circumstances.

In addition to this action, we had an action in front of the Federal Procurement Chamber of the Federal Cartel Office against the health insurer because they had a public tender for the rebate agreement. And the Federal Cartel Office stopped this tender process because it is not in line with patent law.

So again, the theory of unity of the law succeeded. And a third lawsuit was commenced originally in Hamburg at the Regional Court. The defendant was the social securer, the KKH, and the regional court sent the case to the Social Court of Hanover. So the Social Court is the first Social Court judge in Germany was faced to decide a patent infringement case. And he did so as he granted the injunction, but only based on a weighing of interests. So he didn't say a word about patent infringement or about patentability or whatsoever related to patent law.

So what are the unsolved problems at the moment in my point of view? Is the concept of manifest arrangement still applicable at all in the context of indirect infringement as the Hamburg court found? If yes, is the concept of manifest arrangement suitable to provide adequate patent protection in cases of off label use? Because if it's an on label use, it's obvious that we have direct infringement. Is there any reason to grant different or broader scope of protection to an EPC 2000 claim? And is the concept of manifest arrangement applicable to EPC 2000 claims, as we don't have the manufacturing process inside the claim anymore.

So in my view, and of course I know as a judge I had to be kind of reluctant to talk about the future, the court should go on and provide adequate protection to these kinds of invention and think about innovative solutions to the problems at hand. And I think that the Hamburg Court is a perfect example of the way -- for the way we have to go.

Thank you very much.

[Applause.]

HONORABLE KALDEN: Good morning. Thank you very much for inviting me to this conference. I'm very honored. And I won't start off with a table of contents, but I'll pick up where Matthias left us and I will discuss mainly the construction of second medical use claims as we know them and the consequences for infringement.

Before I fire off, I should say, although it's titled The Dutch Perspective, which strictly is correct because I'm Dutch, it's only my personal opinions.

I'm not going to go into the importance of second medical use claims and patent protection, although said yesterday that IP is of no relevance whatsoever, I think it's still common ground that research and innovation should be stimulated and safeguarded by offering patent protection.

The question, however, is just how effective that patent protection is in terms of enforcement and remedies. And in relation to second medical use patents, there are two specific problems.

First of all, the novelty because the compound isn't new. And secondly, the exclusivity from patentability under Article 53(c) EPC for methods of medical treatment.

Now, the first solution, as we've heard before, was in the form of a Swiss-type claim which existed prior to the EPC 2000, which came into form in 2007.

Swiss-type claims are clearly a fiction. In reality, of course, it concerns a new form of medical treatment. The manufacture it's neither new or inventive and it's only there to circumvent Article 53(c), and the real invention only lies in the new use of the known compound. I don't think there's any discussion about that.

The second solution is in EPC 2000, where the purpose-related product claim was introduced compound X for the treatment of indication Z. And as from 2/2/08 in the inter peer case, the enlarged board said that no longer Swiss-type claims would be allowed.

Now, the question is how to construe these claims. And on the face of it, Swiss-type claims are purposely limited process claims and EPC 2000 claims are purposely limited product claims. The difference being the element for the manufacture of.

Now, the question is, do they for that reason have a different scope of protection? Now, I think we're all familiar with the judgments of Richard Arnold, which he delivered on 21st January and 2 February in the pregabalin cases. And he took the view there is a different scope of opinion, and he relied mainly on the decision of the Technical Board of Appeal in the University of Texas Board of Regence case, and in his judgment, striking out the claim for indirect infringement is simply hopeless. He also referred to some earlier U.K. cases, especially Monsanto and Merck 2000, which he suspects is not going to be over ruled by the Supreme Court.

Now, UK's law of course is not binding on other judges than U.K. judges. But EPO case law is, although not binding, considered to be quite relevant by the national courts and are generally followed unless there is good reason not to.

So I think it's necessary to look into the case more closely. Now, as I said, the TBA held that Swiss-type claims and EPC 2000 claims do have different scopes of opinion. But in considering what relevance and consequence that case has to be, it's relevant to note that this decision was taken into context of double patenting. There was a Swiss-type patent that was granted and now an EPC 2000 divisional claim was under consideration. And the examination division refused to grant the divisional application on the ground it related to the same subject matter as the parent application. And it says they concern the same invention claimed in different format.

Now, the TBA, although it recognized that both Swiss-type claims and EPC 2000 claims fill the same gap in the legislation, and that the reason for introducing 54 Article 5 in EPC 2000 was to create legal certainty in relation to the patentability of second medical use claims, and doubts as to the validity of Swiss-type claims existed, it still referred it to the general principle underlying the EPC that a claim to a particular physical activity confers less protection than a claim to a physical entity.

So much importance was attributed to the fact that both claims, solely based on the wording, belonged to a different category, i.e. purpose-related -- process and product claims respectively and therefore, had different scope.

Now, the technical board did refer to the earlier board decision that abolished the Swiss-type claims, but in my opinion, there's nothing in that decision that suggests that the two claim forms must have different scope of protection. And possibly even there is a suggestion to the contrary.

In that decision, the enlarged board first sets out the extraordinary background of Swiss-type claims. It said the earlier ruling introducing the Swiss-type claims found its cause and effect that the claim directed to the use of the substance or composition for the treatment of the human body was forbidden.

And further on, since the intention of the legislator was clearly not to exclude second therapeutic indications of a known medicament from the field of patentability, the so-called Swiss-type claim constituted the adequate but exceptional solution.

The enlarged board then refers to the new provision provided for purpose-related product protection, noting with reference to the preparatory document, that it closed the loophole existing in provisions of the earlier EPC. And the enlarged board also noted that the manufacture element in Swiss-type claims was considered problematic.

It says, Swiss-type claims could be and have been considered objectionable as regards to question as to whether they fulfilled the patentability requirements due to the absence of any functional relationship of features conferring novelty and inventiveness, if any, and the claimed manufacturing process.

Now, most importantly, it also expressly referred to the preparatory document. Now, what did this document say? There it said the new article eliminates any legal certainty. It unambiguously permits purpose-related product protection. This protection is equivalent as far as the further uses are concerned to that offered by the Swiss-type claim. The new articles expressly limited to specific use. This limitation is intended to match as closely as possible the scope of protection to the scope provided by a Swiss-type claim.

Now, that's quite clear language, isn't it? However, the Technical Board of Appeal chose to neglect it and in my view, they wrongly considered these considerations merely expressing the intention by the legislator, which apparently in the opinion of the TBA, apparently had not materialized in view of the general principle that product claims have a broader scope of protection than process claims. But it fails to take into account the background of Swiss-type claims, where the element manufacturer, which qualifies as a process claim, was only introduced to circumvent the prohibition to protect medical treatments.

So taking that into consideration, in my personal opinion, there is very strong argument to construe a Swiss-type claim effectively as a purpose-related product claim. Remember the claim construction should take place in accordance of Article 69 EPC and their protocol.

Now, construing a Swiss-type claim as a product-related -- purpose-related product claim, in my view, stretched the right balance between the legitimate interest of the patentee and legal certainty of third parties. Novelty and inventive step lie in the actual purpose i.e., the therapeutic new use. So that element should be the determining element factor in considering the scope.

And as to legal certainty, it's generally known that a Swiss-type claim is a legal construct where the manufacturing element has only been added to circumvent the prohibition of 53. Or in the words of [unclear name] your Hoffman and Karen Angin, construing a claim, once you ask how would the skilled person understand the patentee was used in the language of the claim to mean. Well, certainly he meant to protect the actual invention. The actual invention is a new use. Manufacturing has got nothing to do with the invention.

So is there a legal objection to this approach? Well, I think not. Novelty is confirmed by the new use. And Article 53, second sentence says that the provision, the exclusion from patentability of medical treatments, shall not apply to products in particular substances or compositions for use in any of these methods.

So where does this lead us for scope of protection? Well, in my opinion, this leads to the situation where if a manufacturer or distributor at the time of manufacture of distribution clearly designates the medical need for the use for the patented indication, e.g. by prescribing the suitability for that indication in the patient, that is a direct infringement. It's an act of indirect infringement if the manufacturer knows or should reasonably perceive that the medicament is going to be used for the preferred indication further down the chain. And he nevertheless continues to manufacture and deliver the medicament without taking any measures to prevent that from happening.

Now, as to intention, should there be some sort of culpable intention to use the generic's medicament for the patented use down the chain. I think that was suggested by Richard Arnold in his judgment, but I don't agree.

If you look at Grimme, which I think it's a U.K. case, but it's a European leading case on indirect infringement, the only requirement is that the ultimate users will intend to put the invention into effect. But intent in that sentence doesn't mean willfully. It only means something that they are planning to do as opposed to something that has already been done.

So requiring culpable intention downstream is wrong and leaves the holder of a second medical use patent without any protection. Because the doctor knows the active ingredient is for the patented indication, but he doesn't intend to use it, specifically, the generic medicament, nor has he any knowledge what product will eventually be dispensed because he's prescribing by generic name.

Reversely, the pharmacy has a strong incentive and intention to dispense the generic product, but usually doesn't have any knowledge what indication it is prescribed for.

So if you would require intention just by one person specifically related to this product by this particular generic company, would leave the holder with a second medical use patent empty-handed. The only thing that's required is that ultimately, if the patient swallows the generic pill for the patented indication as a consequence of the consecutive actions by the doctor and the pharmacy, that constitutes use of the patented invention, which is intended, because it's intended to cure the indication that the patient has.

Now, to close it off. An alternative claim construction advanced by Floyd is that it's also a direct infringement not only if the manufacturer knows, but also if he should know or foresee, so constructive knowledge, that the product is going to be used for the patented indication.

Well, that alternative I think does not solve the problems in the same way as the approach that I think is also a reasonable approach to claim construction. Because in that construction, the claim will still be construed as a process claim. And there are several issues in relation to that which are problematic.

For instance, who is considered the manufacturer? If the manufacturer is based in India and the packaging done in Bulgaria and the distributor is in the U.K. or the Netherlands, who is the manufacturer and whose knowledge or constructive knowledge counts.

In the U.K., in the pregabalin case, I think we should realize that Actavis choose not to distinguish between its knowledge and that of the actual manufacturer. But in other cases, the generic company may raise the argument. There's no -- there's no security that in that case, the actual distributor will be found to have the relevant intention.

So what happens if the manufacturer only intends free use, and the pharmacy knowingly dispenses for patented use or the distributor distributes with the intention for the patented use, is it not an infringement? Because they are not manufacturing.

Reversely it's also a problem. If the manufacturer intends patented use, then how about the pharmacy, who's not dispensing for patented use, would still be infringement because it's product which derives directly from a patented process. Well, I believe these problems and this lack of actual protection is not what was issued and nor intended when Swiss-type claims were introduced. And it may require some courage to construe a claim phrased as a process, as a product claim, but for all the reasons I gave, I think it's better to approach to second medical use patents. And they are already facing enough problems in terms of remedies.

And I'm going to hand it over now to Simon Cohen, who's going to go into that next.

[Applause.]

MR. COHEN: Well, I'm afraid I have to start my presentation this morning not with a joke but with an application and/or just as Jacob. I'm not sure whether he's actually sitting this morning. But a lot of my topic was taken by some of the previous speakers. I'm happy to name names but this is clearly unacceptable. This is an application for trespass on my rights. And I don't know whether Justice Jacob, my Lord, would like to hear me now or hear me maybe over the short adjournment.

SIR JACOB: You have a very strong case. I have to hear the other side of course.

MR. COHEN: Jin, do you want to come forward? Thank you very much, my Lord.

And seriously, I did want to say on behalf of myself and our Taylor Wessing colleagues here to thank the Washington University and Sir Robin. And Sir Robin in particular has done an amazing job taking forth the coalescing as he does the cutting edge scientific developments with developments in IP law. And one thing about Robin is he will take an idea with such tenacity that he will take it forward, just have a discussion for a day or two and leave it. And I know a topic like this, which he's brought us all to discuss, which has been fascinating, he won't give up on and he'll get the commission involved, get the governments involved because that's obviously what's needed rather than merely talking about it.

So we're very grateful in England and in Europe for everything that Robin is doing for the IP community.

Turning, then, to my talk, a lot has been covered so I'm going to sort of take things relatively quickly. The topic of course was remedies for infringement used patents, new use claims of patents. And I'm going to look at the available remedies through the prism of the pregabalin case in the U.K. that Rian and others have spoken to a lot.

And I think the one thing that strikes me, having thought about it and heard the discussions, is that remedies are really a bit of a mess. There's no excuse for the mess. Because I mean we've been speculating about what's going to happen in this situation where there are second uses and legitimate uses and what's going to happen when a generic launches a skinny label. We've been talking about that for years. And therefore the uncertainty and all the various applications required in the pregabalin cases seem to be unnecessary. And one can only hope that it will be cleared up before the next pregabalin comes along.

We've heard all about Swiss form claims. The claim in question here in the box is the use of pregabalin for the preparation of a medicament for treating pain. I'm not going to go through article 53(c) and Article 4 because I think you've all heard about that.

The situation is, as of course we well know, that epilepsy and GAB were not subject to patent protection at time at launch where pain still did have patent protection. And one of the generic companies wanted to launch a skinny label and what was going to happen.

So as sure that X was X, no great surprise, as soon as Actavis planned -- made clear they were trying to go into skinny label, Warner-Lambert sought interim relief.

Now, what's interesting, as I understand it, they didn't ask for a preliminary injunction, a straight out and out injunction, but they asked for all sorts of conditions as part of their interim relief. They asked that they should make it a condition Actavis having any agreement with pharmacists they shouldn't prescribe it for the patented use. They asked them to write to the superintendent pharmacists, and Jin explained the structure in the U.K. of all various organizations involved, the superintendent pharmacists, the CCGs, the clinical commissioning groups.

So they wanted everything to be done to try and ensure that the generic product would not be used for the patented indication, which seemed fair enough. That was the relief they sought.

Another bit of relief sought was that Actavis should put removable cellophane wrapping over their product, stating it was not authorized for the treatment of pain and must not be dispensed for such purposes. So a whole long list of requirements that Actavis sought to obtain. And Mr. Justice Arnold, in all his glory smiling down at us, he's sorry he can't be with us today I'm sure, said no serious issue to be tried and his formulation for infringement of a Swiss form claims, as a purposeful claim as we heard, was that it requires a subjective intention, objectively assessed on the part of the manufacturer that the product would be used for treating the patented indication.

In any event, the judge didn't find infringement. He also found the balance of convenience favored Actavis and no interim relief was granted.

The next story in the interim relief sequence of events was that Pfizer attained -- made an application for NHS guidance. They obtained an injunction against the NHS, the British National Health Service, requiring them to instruct doctors to prescribe pregabalin, the generic pregabalin, only for the nonpatented stuff, and that they had to use and dispense Lyrica when they were treating neuropathic pain. So that came out. That was guidance along the way.

Arnold entered an injunction application, then went to the Court of Appeal and Lord Justice Floyd also rejected the application for interim relief for all the various conditions that Warner-Lambert had wanted. He also held the balance of convenience was in Actavis's favor.

But after we heard, he came up with a brand-new formulation for infringement. He said infringement of a Swiss form claim requires that the manufacturer knows, constructive knowledge being enough, or can reasonably foresee the ultimate intentional use for treating the patented indication.

So clearly an easier task to fulfill for the patentees rather than the Arnold test but very different.

Just to see how the system works, of course, the case that went on to a full trial but its validity, which I won't touch upon, and also on infringement, Mr. Justice Arnold commenting on Lord Justice Floyd's formulation of infringement, said, I have considerably backed into the correct method of Lord Justice Floyd's interpretation. Great respect here from one judge to another. Nevertheless, I cannot say that I'm entirely convinced that it is wrong. Very gracious.

So there you have it, two different infringement tasks really confusion as to what's going to happen when a generic skinny label is going to be launched where there are legitimate and nonlegitimate uses. And it seems to me the mess described is really no good for anyone. It's certainly no good for the generic companies. It's certainly no good for the government national health services. I don't know whether it suits the brands or not. I have a sneaking feeling that the continued uncertainty may actually help the brands somewhat.

What is the solution to the mess? Well, Mr. Justice Arnold in three or four paragraphs of his judgment, that only ran to 727 paragraphs on this occasion, I don't think Rian has ever done a judgment that long, have you Rian?

HONORABLE KALDEN: No.

MR. COHEN: Did offer a number of solutions. And what he was saying is the only way forward is to separate the patented market for the substance from the nonpatented market by ensuring that prescribed -- is write prescriptions for the patented indication by reference to the patentee's brand name and write prescriptions for nonpatented indications by reference to the generic name of the substance, the INN.

So he's talking about separating the market so that it's clear that whenever a prescription is written and subsequently dispensed, you know what the ultimate indication is.

The problem is certainly is the way the U.K. is set up; the software doesn't exist. The pharmacists don't know exactly what they're dispensing for. And Arnold hopefully, I think rather hopefully, calls upon everyone, the patentees, the generics and the government to try and change the system so that there is a complete separation of the markets. And he ended the judgment by saying, I therefore trust that the Secretary of State will take steps to ensure that a suitable system is put in place in England.

Just by finishing, I have to say I have reservations that the government will do anything. I think we may need Robin's pushing on this because as Robin reminded me yesterday when we

were talking, even though the NHS loses tens of millions of pounds whenever there is a wrongful preliminary injunction granted, they hardly ever -- they never did get involved in the litigation, even though they were written to, they were asked to come to court. They could never be bothered, and it was only as a result of Robin's encouragement, I think in the first Paroxetine case, that it's now part of our procedure in the U.K. that the NHA automatically gets the benefit of any loss it makes under the cross-undertaking.

So I think that would be a great step forward if the Secretary of State and the government got properly involved in these cases, because it means that they would get compensation for the money lost. Because it would reduce the incentive for the patentee to go for the interim injunction in the first place. And I think everything would be fairer all around.

All on that, thank you very much, and I will adjourn my application to Robin.

[Applause.]

HONORABLE IIMURA: Good morning. I'm very honored to be invited to Remedies for Infringement of New Use Drug Patents Session.

1. Patent infringement suit involving a drug for a certain use:

(1) "Claim construction" for "a claim on a product reciting the use thereof"

The main issue is how to construe the exclusive scope of a patent right for a "Drug comprising compound A as an active ingredient for the treatment of disease P." In Japan, the dominant view is to narrowly construe it as "to manufacture and/or sell a drug A to be used for the treatment of disease P," as the claim language literally provides. There is no view to construe it broadly as "to manufacture and/or sell a drug comprising compound A."

In other words, where a product patent (drug patent) recites a certain use in the claim, the Japanese claim construction practice is to limit the technical scope to such a use.

(2) Difficulties for a patentee in enforcing the patent right in a patent infringement suit based on a drug patent reciting the use, a patentee would be faced with the following difficult issues.

Assume the following case: A plaintiff pharmaceutical company seeks an injunction against a defendant pharmaceutical company enjoining from manufacturing and sales of the accused product based on a patent right related to "drug A for the treatment of disease P."

The defendant would make a counter-argument as follows: although the accused product is an identical compound to the patented drug, the accused product may be used not only for the treatment of disease P recited in the claim but also for the treatment of other diseases (such as disease Q), and indeed it is used for such other purpose; therefore, the plaintiff's claim has no ground, since the accused product is a drug sold for the treatment of disease Q and indeed is used so.

I will address the analysis based on a premise that such a drug is "an OTC (over-the-counter, non-prescription) drug," which is different from "a prescription drug" that is prepared by a pharmacist based on a prescription provided by a medical doctor.

In such a case, it is impossible to identify how a purchaser uses a drug for the treatment of a disease. It is a matter of what the purchaser decides, and the defendant cannot identify how the purchaser uses the drug.

Therefore, it is almost impossible for the plaintiff to prove how a patient who purchases the accused product uses it for the treatment of a disease.

Under these circumstances, various standards have been suggested as to how to determine the issue as follows.

2. Various standards

(1) Label theory: To determine in accordance with what is described on the label.

In terms of non-prescription drugs, infringement or non-infringement is determined by whether a label that describes the efficacy of a drug includes "for the use P," where the label is usually shown on a container or package of the accused drug that a defendant Y sells.

Such a theory dramatically reduces the plaintiff's burden, when compared to the general one where the plaintiff must prove how a patient uses a drug and for what purpose in reality.

This theory is popular in Japan, maybe because, by relaxing the plaintiff's burden, it considers the balance between a patentee and a defendant to find a fair solution to the dispute.

It must be noted there is a hotly-debated issue in the detail. Basically there are two split theories as to what kind of description is required on the label:

(A) The label describes the use P.

Infringement is established as long as the label describes the use P and it does not matter if the label also describes the use Q.

(B) Another use Q is described in addition to the use P.

Non-infringement is found if the label describes not only the use P, but also another use Q (since there may be a possibility that a patient purchases the drug for another use).

The former view is more popular, which favors the plaintiff. As long as the use P is described on the label, patent infringement may be established. However, there are two major criticisms: First, it is too formalistic; and second, a defendant may easily circumvent this theory by not describing "the use P" on the label, which inevitably limits a patentee's right to enforcement.

In particular, the impact would be significant where a patentee is granted a patent for the second use in addition to the one for the first use, although the first patent has expired.

(2) Totality of circumstances theory: To determine by the totality of circumstances such as sales activities with respect to characteristic features of the accused drug and the like.

Because of the criticism that the label theory is too formalistic, this theory emerges. This theory is based on the totality of circumstances, such as how the defendant provides a technical explanation of the accused drug, how the defendant engages in sales activities, and the like.

(3) Personal view

I personally advocate for the totality of circumstances theory. The label theory is simple and easy, which may relax much of a patentee's burden. However, it may not necessarily favor the patentee, because as mentioned earlier the defendant may easily avoid infringement by not describing the use on the label or package.

Therefore, it is reasonable to draw a conclusion from a substantive view, considering the totality of circumstances, such as how the defendant provides a technical explanation of the accused drug, how the defendant engages in sales activities, and the like.

3. Court decisions

(1) Tokyo District Court decision dated October 23, 1992

This court based its decision on the label theory.

(A) Factual background

The patentee had a patent entitled "preventive drug for bronchogenic asthma comprising compound A as an active ingredient." The plaintiff sought an injunction enjoining the defendant from manufacturing and selling "drugs comprising compound A, used by oral administration after breakfast and before bedtime, for preventing 'bronchogenic asthma.'"

The defendant's drugs were not prescription drugs but OTC drugs sold to general consumers. The defendant's drugs had a description on the container stating that it was effective not only for "preventing bronchogenic asthma" but also for "preventing sinus infection."

(B) Court's decision

The court awarded the injunction claim in favor of the plaintiff. The court held that a patent infringement was established since the accused drug displayed the description stating that it was effective for "preventing 'bronchogenic asthma' and 'sinus infection.'"

The decision is considered to be a court decision that supports the label theory.

The court also addressed whether it is sufficient if the label describes the use P or if it is not sufficient if the label describes another use Q in addition to the use P. The court held that in order for a defendant to defend against a plaintiff's claim, the defendant is required to prove not only that the accused drug is substantially effective for "preventing sinus infection" but also that the accused product describes "the efficacy is excluded for preventing bronchogenic asthma."

In this regard, the court took a restrictive view with the defendant, requiring the sales be made with the label description excluding the use Q in order to avoid infringement liability.

(2) IPHC decision dated Nov. 21, 2006

Unlike the above Tokyo District Court decision, the IPHC adopted the totality of circumstances theory.

(A) Factual background

Under the Japanese Patent Act, where an employee makes an invention related to work and the employer is assigned the employee's invention, the employer is obligated to pay reasonable compensation to the employee-inventor (some revisions have been made to this provision since however). In this case, the plaintiff (the defendant's employee) sought reasonable compensation from the defendant (corporation). Although it is not a genuine patent infringement suit, it may be treated as a precedent, since the court determined whether or not the defendant worked the patented invention.

The plaintiff's invention related to a "preventive and treatment drug for arterial occlusion by substance A."

(B) Court decision

The IPHC held as follows. "The defendant did not sell the accused drugs comprising substance A, described explicitly as a 'preventive and treatment drug for coronary arterial reocclusion.' However, the defendant actively advertised and engaged in sales that the accused drugs have an efficacy of preventing arterial occlusion and the like. Such acts by the defendant were determined as falling under the working of the patented invention." The court upheld the plaintiff's claim.

In other words, the IPHC in this case came to its decision not by whether or not the label on the container or package described such a use but based on the totality of the circumstances.

4. Conclusion

The foregoing discussion can be summarized as follows:

(A) The scope of exclusivity on drug A upon discovery of a new use P is limited to the manufacturing, sales, etc. Of drug A for the use P recited in the claim. It does not extend broadly to the general "manufacturing, sales, etc. Of drug A."

(B) The plaintiff bears a difficult burden to prove that the accused drug that the defendant company sells is actually used for the use recited in the claim.

Therefore, some courts hold that it is sufficient as long as the accused product describes the claimed use on the container or package.

(C) Furthermore, other courts hold that, although there is no description of the claimed use on the container or package, the plaintiff may prove that the accused product is used for the claimed

use by the totality of circumstances such as how the defendant engages in sales activities, advertising, and providing technical explanations, etc.

5. Supplementary remark 1 (FDA-like approval)

As mentioned earlier, my presentation is based on an OTC drug. I would like to supplement this in terms of the FDA-like government approval process.

In order to manufacture or sell a drug, the following processes are required.

(A) A pharmaceutical company is required to obtain government approval for manufacturing and selling a drug

It is necessary to apply for the approval by identifying the safety, efficacy and effect of a drug. Once it is approved, a pharmaceutical company is permitted to manufacture and sell the drug as approved, and is prohibited from manufacturing or selling beyond the approved scope. (B) For a prescription drug to be provided to a patient, a doctor's prescription and a pharmacist's preparation are required. In the case where the doctor's prescription says "the brand name of a certain drug," it would be impossible or difficult to provide a patient with "a drug" of another pharmaceutical company.

In the case where the doctor's prescription says merely "a generic term by the name of an ingredient," the pharmacist may freely select any drug, whether it is the plaintiff's drug or the defendant's drug.

In the latter case, a pharmacist (or a seller) may be a possible defendant. (In reality however, it is not practical for a pharmaceutical company to sue the pharmacist.) (C) In contrast, in the case of an OTC drug that does not require a doctor's prescription, a patient has a freedom of choice (own discretion) whether or not to purchase the plaintiff's drug or the defendant's drug. However, where the plaintiff's drug and the defendant's drug share the same substance, it is not usually clear whether the patient uses a drug for the use P or for the use Q. (D) Therefore, there are a number of unresolved issues concerning how a patent right is enforced on a new use drug.

Note: A prescription drug is defined as "a drug that is provided based on a diagnosis by a doctor, etc. To look for a relevant treatment policy, that may not be used safely and effectively unless an appropriate choice is made depending on a patient's medical condition, predisposition, and the like, due to difficulties such as ease to cause a resistant strain or a complex administration method, and government approval." 6. Supplementary remark 2 (Patent eligibility where compound A was discovered effective for the treatment of disease P)

I will not address the patent eligibility on a second use discovery for the same compound, since another panel will discuss it.

The present Japanese practice on the topic is as follows.

(1) Product patent

Where compound A was discovered effective for the treatment of disease P, a product patent may be granted. (A) If a discovery is made for the first use Where compound A was discovered effective for the treatment of disease P, "a product patent" may be granted.

The claim would be described as follows: "Drug comprising compound A as an active ingredient for the treatment of disease P;" or "Drug A for the treatment of disease P."

(B) If a discovery is made for the second use

In addition, if the same compound was discovered to be effective for the treatment of a totally different disease Q,

"a product patent" may be granted as well.

The claim would be described as follows: "Drug comprising compound A as an active ingredient for the treatment of disease Q;" or "Drug A for the treatment of disease Q."

(2) Method patent

In general, in Japan, a patent may not be granted for a treatment method.

The reasons are as follows: (1) since an injunction would be sought against a medical doctor based on patent infringement, it is not appropriate to seek an injunction against a medical doctor taking into account the adversarial impact on a patient; (2) since "medicine" is not regarded as an "industry" subject to patent protection, a treatment method should not be subject to a patent, and the like.

Thus, only a product patent is available for such a medicine, thereby a patent infringement suit in this regard is always based on "a product patent."

In addition, it is generally disputed between pharmaceutical companies X and Y. My following explanation is based on such a premise.

7. Supplementary remark 3 (a new use discovery made on an existing non-drug substance)

In Japan, the following practice can be found to determine whether a new use is patent eligible if it was discovered on an existing non-drug substance. (1) Product patent (A) A patent is granted for a product invention for the first use. (YES)

Assume a person discovered that substance A is effective as a pesticide (killing insects). He may be granted a product patent claiming "substance A for the use as a pesticide." (B) A patent is not granted for a product invention for the second use. (NO)

In contrast, in the case where a person discovers that substance A, that is effective as a pesticide is also effective for weeding, "substance A for the use of weeding," a majority view is that "a product patent" cannot be granted. However, there is the IPHC decision dated Nov. 29, 2006 holding that "a product invention" based on the second use is to be granted a patent. I would say the practice is not necessarily established.

(2) Method patent

(A) A patent is granted to a method invention for the first use. (YES)

In the case where a person discovered that substance A is effective as a pesticide (killing insects), he may be granted "a method patent" claiming "a method for pesticide use by using substance A." (B) For the second use invention (YES)

In the case where a person discovered that substance A is effective for weeding in addition to the prior art showing it is effective as a pesticide claiming "a method for weeding by using substance A," the person may be granted "a method patent."

A product patent is very strong, so it is not appropriate to grant a product patent just for the discovery of the new use of a certain substance except medicine. On the other hand, it is reasonable to grant a method patent to discover the new use of a substance.

We have lots of answers among us, but my explanation is I would like to conclude my explanation. Thank you very much.

[Applause.]

HONORABLE BROWN: Good morning. Well, it's still morning although just, and I'm quite aware that I'm standing between you and lunch, so I will try to stay on to my schedule, and I'm sure that David will remind me of that.

Now, my task here is to talk about remedies for infringement of new drug patents. And my first reaction was the remedies per se are the same as for old use patents. What we've been talking about here really seems to be an issue of infringement, or contributory infringement if you have a skinny label carve-out. And I don't want to jump ahead too much. So I should probably discuss the Hatch-Waxman Act, which is our unique contribution to jurisprudence in this area.

Because just jumping ahead for a moment just to encapsulate the problem. I've seen cases where you have a Section 8 carve-out for a skinny label. And I've seen them raised in Hatch-Waxman actions, and there it seems to me it's an infringement issue. And we still have the 30-month stay unless somebody wants to launch risk. So I don't know that that's necessarily going to distinguish it one way or the other.

Now, to get back to the earlier context and put it all into perspective, I'll start at the beginning. Article 1, Section 8, the U.S. Constitution authorized congress to enact laws giving investors exclusive rights to their discovery as inventors, certainly after that judiciary act of 1789, and the first patent act.

So we had the executive branch issuing patents. You had the rights enforced in the federal courts. That's still the case today. You could go back and have your patent re-examined. It took some years under the American Invents Act, it moved ahead into partes review, where you could have a review that would come in the matter of months rather than years. It doesn't seem to have been used as extensively in the pharma area as it is in certain other areas, Mr. Bass notwithstanding.

And then of course you can have -- or seek to have the ITC exclude infringing pharmaceuticals and move on a faster pace, but you don't really get any remedy other than a limited or general exclusion order. You don't get damages. You can get a cease and desist order.

Again, the primary focus has been the United States District Courts, which is more of a generalist body than I'm hearing from the other jurisdictions.

Now, I don't mean to say generalist in terms of general jurisdiction, because the federal courts have limited jurisdiction, although congress expands the limits fairly frequently.

So what do we have? We have a court that is handling everything from antitrust and admiralty to zoology and zoning and everything in-between. And there, in along everything else, come the patent cases and of course that's only the civil side.

Those of you that have had cases in the district court probably had the experience of a judge taking a break all of a sudden the door opens, and a Deputy United States Marshal walks in -- and yes, we still have U.S. marshals -- marshal will walk in with a bunch of people with orange jumpsuits on looking rather shifty wearing handcuffs and there you're introduced to the criminal side.

So we have a court handling both civil and criminal, a variety of things taking on the challenge of patents as they have for many years. I mean for example, the Wright brothers, Robert Fulton, Thomas Edison, where did they all go to enforce their rights? United States District Court.

So we have a very active patent docket, some courts more active than others. Our court in New Jersey is extremely active in the pharmaceutical area. I came on the bench in '86, and all of a sudden I was confronted with a new statute, the Hatch-Waxman Act, which created a whole new regimen. You had a concept really of a statutory or constructive infringement where the generic couldn't -- didn't have to launch at risk as it were, and take the chance of having damages assessed, but could piggyback on the new drug application of the branded, the innovator with an ANDA, and of course wind up with the ANDA being filed, notice to the manufacturer, and you've got a period of time there for a suit to be filed. Which was really a mirror image of general litigation, because the defendant was the one that started the whole thing.

When we changed our rules, we noticed this fact and made the defendant explain what was going on there to the branded, who did not necessarily know as much.

Then of course you have the 30-month stay. And that was the reason why I raised this question. Because if you're going to have the 30-month stay in any event, whether it's a carve-out

or some other claim of noninfringement or invalidity, I think you're going to go through the same practice.

Would you agree with that not, David?

MR. TELLEKSON: I think that's right.

HONORABLE BROWN: Okay. So we have a different regimen in the United States, as I say, which gives you certain period of market exclusivity that are not expressly patent-based.

We have a 7-year exclusivity for orphan drugs, a 5-year exclusivity for new chemical entities, a 3-year exclusivity for new clinical studies where you have the approval leading to new or changed formulation, dosing regimens or patient populations. Which is exactly what we seem to be talking about here. So you have that protection right there.

Now, you also have the possibility of a 6-month PD exclusivity if the FDA requests that the NDA holder conduct studies in pediatric populations. So you do have that.

On the other hand, you have the generic and ability to challenge the patent without having to put themselves at risk unless they wish to do so. And you have of course an extension of the patent for FDA delays and approval.

So what we're seeing in the courts is primarily the Paragraph 4, the way of challenging the patent as being invalid or not infringed. That's -- and of course the court had to move along a lot more rapidly than we had before, because you have this 30-month stay that expires, and then all of a sudden you're faced with a preliminary injunction. We've done pretty well on moving them along but we do sometimes face that.

Why does the generic want to do this? Well, of course congress encouraged them by saying you've got 180-day exclusivity. You'll be the first to launch if you do this. There have been some cases where there have been two generics that are filed on the same day to avoid unseemly jockeying, pushing someone out of the way. If they file on the same day, they both get that exclusivity period. It can be forfeited under certain circumstances, but which is set forth in the statute, but generally not done so. As I said, we adopted procedural rules to deal with this during the 30-month stay to keep things moving.

Of course if the branded does not file suit as required in 45 days, then the 30-month stay is not available. But the generic can go forward and seek a declaratory judgment at which the trial, well, you know, there's a couple features of U.S. jurisprudence which would be different. One is the right to a jury, and two is the lack of a right to attorneys' fees. In the Hatch-Waxman context, which we're dealing with in pharma, assuming there has not been an at risk launched, there is no damage. Therefore, the entire issue, validity, infringement, will be tried to the judge alone.

On the other hand, if you do have an at risk launch, now you've got the jury handling both of those issues with instruction from the court. So as I said, attorneys' fees, even though they may rise up in the 7-figure range, are not going to be awarded absent an exceptional case. And there's been some jurisprudence on what constitutes an exceptional case.

So what is the relief that you're seeking? Well, assuming that that judge has not moved forward in 30 months, the brand might be seeking a preliminary injunction. U.S. law favors multifactor tests. We got a four-factor test for that. Likelihood of success on the merits, media irreparable injury, balancing the hardships and the public interest.

Permanent injunction at the end of the trial change the factors a little bit. Has the patent owner suffered an irreparable injury? The remedies of law such as monetary damage is inadequate compensation. The bounds of the hardships and the public interest.

Before the Supreme Court spoke and Mr. Stoll told us about a number of Supreme Court decisions in his excellent presentation, but before they spoke, in eBay, there was a feeling that you

were entitled, as the owner of the patent, to exclude competition, period. Even if you were not practicing.

Supreme Courts have known patent cases, federal lawsuits like other federal lawsuits, you have to go through the four factors. It may be that they favor you; it may be that they may not. But that analysis is now done in all circumstances.

If there is monetary damage, the generic has launched, then we get into questions of reasonable royalty, possibility of lost profits, profitability of market erosion. And again we've got factors, Panduit factors, for example. We like those factors.

And as I said, costs are not going to be awarded absent an exceptional case.

So those are the primary differences. As I said before, I see the question of the Section 8 carve-out, the skinny label, as being one of infringement, be raised generally in my Hatch-Waxman context and not a matter of remedies per se, at least in the United States.

So those are the points that I -- I assume I'm within my time? Those are the points that I raised. I'm going to be available for questions.

And I think that -- when Sir Robin asked me to speak, I thought, well, okay. I'm not a pharma expert. I'm not a patent lawyer. I'm a generalist judge. As you can see from the background, yes, I've had hundreds of pharma cases, I've also had thousands of other cases, everything, class actions, multidisciplinary litigation and the like. So what perspective could I bring on this? Well, I guess the perspective of someone who sees what the courts do day in and day out in one of the busier of the pharma patent dockets, and give you the perspective as to how the courts face these issues in the United States. And I'll be happy to provide that perspective for you. Thank you.

[Applause.]

MR. TELLEKSON: Thank you, everyone on the panel. I've got some questions for the entire panel but -- and it may be a little off topic, but Judge Brown, you mentioned the right to a jury trial in the United States. And I think a lot of people in room think we're nuts that we actually entrust complex patent cases and other cases that involve lots of complex technology. In your experience, how do juries do with these complex scientific issues?

HONORABLE BROWN: Well, for one thing it's again a matter of constitutional right. The Seventh Amendment guarantees the right to a jury trial if you have legal as opposed to equitable relief. I think injunction is equitable relief. Only injunctions or only judge. Damages sought goes to the jury. The juries try to do the best they can. And I will say that usually, I agree with their determinations. I've had some jurors on, some with a technical background, some of whom got very interested in the case. I've also participated in some mock jury exercises from time to time and sometimes having watched it, I'm reminded of the remark attributed to Bismarck, that you don't want to watch legislation and sausage being made. So you may not want to watch jury deliberations.

But on the whole, I think that really it brought out a new talent in the IP bar as we saw an increasing number of infringers demanding a jury. And that was the -- I guess the old-fashioned trial lawyers, someone who could break it down and simplify it to the jury. Not dumb it down, but simplify it. And when I instruct the juries, I say this may be a complicated case to you, but you will understand it because the lawyers and the witnesses will explain it to you. Hint, hint, that's your job.

So I will say that I've found that jurors usually get it right. Maybe their thought process is not what a trained lawyer would follow. But you can also have specific jury interrogatories taking them through point by point, question by question, claim by claim to focus them on issues. I've used that very effectively.

MR. TELLEKSON: Thank you. My experience is they do a remarkable job and kind of surprise you with how well they understand things as long as the lawyers keep it simple or explain it well.

To the entire panel, we've been -- I want to talk a little bit more about remedies and when they're available and in particular injunctions. Can you think of instances where there's a finding of liability, there's a finding of infringement, whether it's on a first use patent or second use patent, but an injunction is not the appropriate remedy? What sort of factors come into play when you decide that you're not going to enjoin the patent infringer? Anybody want to take that one?

HONORABLE KALDEN: Well, I can say this. In the Dutch Court of Appeal case, which dealt with a preliminary injunction, the situation was rather clear. Because the patented indication to 97 percent of the market and the free indication, only 3 percent of the market. So under those circumstances, although, you know, 3 percent should remain free, we still decided to issue an injunction or indirect infringement.

Now, of course that injunction doesn't say they shouldn't supply any of the products anymore. It just says you should stop indirectly infringing. And of course indirect infringement has this concept of knowing it's going to be used and not doing anything about it.

So clearly there was an obligation on the defendant in that case to make sure that that wouldn't happen any further. And of course one of the arguments was well, you can't -- your court can't issue an injunction because that's bound to end up with enforcement disputes. And of course that's a possibility. But still we thought well, that's up to the responsibility of the parties, and especially the defendant, to make sure that he's not in breach of this injunction. But that again was quite a clear case. And I can imagine if the situation would be different, you know, like the reverse situation, like 50 percent, 40, 60 percent, those are very difficult cases I think to issue an injunction because that would mean that almost half of the market would be blocked, whereas half the market would be free. And it would be a less clear situation of, you know, foreseeability that your product would be used for the patented use.

So yes, whether or not you issue an injunction very much depends on the circumstances.

MR. TELLEKSON: How would -- how would that company selling to the 3 percent market, what could they do to show that they're not foreseeing? Don't they have a right to sell to that 3 percent market? How can you enjoin them from selling in general?

HONORABLE KALDEN: Well, very similar to the German case, they participate in a tenet procedure with the insurer. And they were selected to be the preferred supplier, which means that for every indication, their product would be used. So you can be sure that your product is also going to be dispensed for the patented indication. So they shouldn't have participated in this tenet procedure without any reservation as to their product would only be used for the patented disease and not for osteoporosis. So that's the first point.

Secondly, they did send a message to pharmacies saying, our product shouldn't be used for -- shouldn't be dispensed for osteoporosis. But they started off this letter by saying, this is a formality. Full stop.

So I mean you can't take that serious. So you know, there should be some more real effort to make sure that the indication that its patented is really protected.

MR. TELLEKSON: Judge Brown? Anyone else?

HONORABLE BROWN: Sure. Well, again, in the United States it's balancing the fact is the injury irreparable? Is it compensatory monetary terms? Are we dealing with a nonpracticing entity? Are we dealing with an entity that has licensed this or offered to license beforehand? And we know it's compensable in monetary terms. There's an entire industry that has developed by the

experts, as you know, in the damage area, Georgia-Pacific factors, Panduit factors. All of that is considered the balance of the hardships, the public interest. The public has a strong interest in an effective patent system, but it may well be that somehow this drug will not be available to the public. Maybe the patent owner doesn't have the capacity to provide it. Maybe there's some other public interest that would say reasonable royalty wouldn't be appropriate. Again, it's very fact-specific.

MR. TELLEKSON: Let's talk a little bit about the public interest. Is the public interest a factor in other countries, in Europe and Japan, in looking at an injunction? Is that one of the factors you consider?

MR. ZIGANN: The German point of view is that when we look at main proceedings, if the patent owner infringement is found, has a right to the injunctive relief. And this right may only be declined in exceptional circumstances.

So for example, if you have this antitrust situation with standard essential patents. I can't think of any circumstances when looking at the problem you're discussing today.

When we look at preliminary proceedings, the judge is very free to grant or not to grant adequate relief. So in the German court, the remedies sought for in Great Britain, as we learned today, would also be possible. So in a milder step to go forward for the time being.

But as the calculation of damages in an indirect infringement setting is very, very difficult under German law. The patent owner is desperate to get injunctive relief because nothing else helps for him. He doesn't want to go for the pharmacist and he definitely does not want to sue the practitioners.

In reality, the pharmaceutical industry is putting a lot of money into the marketing directed to the doctors to convince them to prescribe their products. So definitely we don't want to sue the doctors.

Yeah, I think the German courts are bound to that. So they have to grant injunctive relief. And the only question we could talk about is to what extent. So what actions are exactly enjoined. And as I pointed out in my presentations, we have to make it to see if we have direct infringement or indirect infringement. If it's indirect, we cannot stop the manufacturing process as such. We can only stop putting into the market and offering. And even though it's only put into the market and offering without indicating to the customer that it must not be used for the second medical indication, which is kind of limited, but that's what we are able to grant to the patent owner.

MR. TELLEKSON: Mr. Cohen, the U.K.?

MR. COHEN: Yes. When they file an injunction, and certainly in the pharmaceutical field, Robin will correct me if I'm wrong, I'm not aware of any company not getting injunction with the exception of that Biogen case. I don't remember exactly what happened. Wasn't there a whole public interest issue as to whether or not there should be compulsory license since obviously -- if the patent is not developing it. But basically, unless it's in the public interest that the patients aren't going to get the product, you're pretty well entitled, aren't you, to get an injunction, a final injunction if not a preliminary injunction. Robin.

SIR JACOB: There's not a question. Well, there's an indication in one case that a final injunction might be withheld if, for example, the patentee can't supply the market. And we've just had a decision where the patentee decided not to ask for an injunction straight away because the patent is so big. It's big pharma against big pharma, so nothing to do with the subject we're talking about. But the patent is effectively been put up for the treatment of cancer, all cancers. It's a second medical use. It's a second use patent.

But there's no product on the market. So we don't get the problems of a cheap product being sold for a new use. And the patentee, BMS, or they have the exclusive license since the Japanese company invented it, Ono, said no, we're not asking for an injunction at the moment. This is how much you have been paid. We're selling it for one thing, you're trying to make it for some other purpose, and we're not going to stop you from doing that. And I think that's just an extra feature.

The big problem we're facing here is Rian has an easy case when it's 97 percent and they intended for the whole lot 100 percent. And you knock them over. And she's right. Well, what if it's 50/50 with 3 percent the other way? And then you've got a real problem about pursuing an injunction. Because an injunction mustn't cover that which is old.

And the real root probably may be to start looking at the payers. And say well, you have to cough up. You are paying for this new use, you know you are.

So it's a bit like the same thing with the Internet when you're looking for pirates, and you start saying well, the bankers, follow the money. I think follow the money is going to be the solution.

And I'll just make my other comment here while I'm at it. You might want to answer this question when it comes up. Is the patent solution system at all relevant to this problem? Half the things or more than half the things you can't patent because the doctors notice a new use and you're following it up. There's nothing to patent, and it's all obvious or anticipated. But what we're looking for is the incentive to follow it up even if it's obvious.

MR. COHEN: Can I get back on that? Because I was talking to someone else, I think to Jurgen about this last night. The patent is not dead. You didn't settle its last remains. High court decision that doesn't quite hit it for the reasons you've said now and previously.

But what I don't understand is why the regulatory system in Europe doesn't give extra protection. And I've never --

SIR JACOB: Hear more this afternoon.

MR. COHEN: Right. But it all seemed to start --

SIR JACOB: We've got a panel.

MR. COHEN: Obviously all the global marketing authorization. But it just seems to have gone too far. I'm a great one for balance, and I'm not attacking anyone. But it seems to have gone too far the other way. There's no beta for the dosages for the indication, for everything, really. And that seems to be the only way to correct it. Rian?

HONORABLE KALDEN: Well, one comment to make is that the generic company in our case also argued, well, you shouldn't injunct us because we are new to the situation by the tender procedure issued by the insurer, which doesn't allow us to make a distinction between patented use and unpatented use. And then we said well, that might be, but then your choice, you know, could also have been to not, you know, go on with this tender or force them to allow you to make this distinction. So we issued two injunctions nevertheless.

I must say, though, the same person, Jurgen, yesterday asked the courts and the judges to be more courageous and allow the proper protection given to second medical use patents.

Well, I tried this morning to advance one possible solution. But the other thing I would like to say is that the pharmaceutical industry should also be more courageous and go against the insurers or go against the regulatory. Because now they're only fighting the competitors and that's not going to help you anyway.

MR. ZIGANN: May I comment on this? In Germany, they went after the insurer and they succeeded. And we will have to wait for the outcome if it's appealed, what the Social Court did. That's going to be very interesting.

And the second point I wanted to add was that under German law, you don't need intent or negligence if you ask for injunctive relief. So it's enough that the infringing acts are commenced by the defendant. And as it is directed to the future, you don't need intent or negligence because now he knows what he's not supposed to do. You only need these two if you ask for damages.

MR. TELLEKSON: David, why don't we open up to the floor at this point. I think we only have five or so minutes so let's open it up to questions from the floor.

AUDIENCE MEMBER: Thank you. I had a question for Judge Brown, and it's in the context of having a discussion with some of the esteemed colleagues from Germany and specifically about NPEs, I think you briefly mentioned nonpracticing entity. And what seems to be apparent is that in the German system, if you're an NPE with a good, solid patent, you get treated fairly. However, here in the U.S., in the district courts there seems to be -- and I'm not a patent litigator but I hear this secondhand -- that there's a tremendous amount of bias. Even if you have good, solid, valid patents and you have inventors who put their passion and their life's energies into inventions, there's still a tremendous amount of bias against an entity that's not producing product. And I'm wondering if you could address this, and perhaps your colleague from Germany could comment. Why do we have this discrepancy? Is it cultural or are there other reasons between the U.S. and Germany, and why can you as an NPE, with a good -- not junk patents but with valid patents, why do you have to face this maelstrom of bias?

HONORABLE BROWN: Well, I don't know that you do. I mean a nonpracticing entity can be a variety of things. It can be a research organization. It can be a university. It doesn't have to be the definition of the troll that has bothered the congress, someone with a junk patent that will assert it and then settle very cheaply to go away. I mean I think that is what the public has picked up. That's what the congress has picked up.

I don't see that perception in the courts. I mean, we understand, there are people that are in the business of research or the people in investing in valid patents, and they have a right to have their property compensated. So I see a distinction between the probius term "troll" and NPE.

AUDIENCE MEMBER: My question is for Mr. Cohen. In the litigation that you described, it seemed like the rule that Judge Floyd originated was pretty friendly to the patent holder, and yet no preliminary relief. What reasons did he give for denying the preliminary relief?

MR. COHEN: I think he found there was -- when Judge Floyd denied the injunction, I think he found there was no serious issue to be tried because there had to be intention on the part of the pharmacist.

HONORABLE KALDEN: No, I'm sorry. I think he denied the injunction on the balance of interest. Because there this order with the National Health Service who issued an instruction to the doctors prescribing that they should be prescribing by brand name if it was for pain. And since that wasn't in place, there was no real risk of any further infringements. So that was the reason.

AUDIENCE MEMBER: Thank you.

SIR JACOB: It didn't work of course, but never mind.

HONORABLE KALDEN: Well, that was the reason.

AUDIENCE MEMBER: Actually, sorry, I've got a copy of the decision here. And basically I think neither of you are actually right, I'm sorry to say. Basically, as was set out by Jin earlier on, the test is if the issue is to be tried and in regard to the balance of convenience, and Lord Justice Floyd said there was a serious issue to be tried, but he said actually the judge properly evaluated the evidence on the balance of convenience, therefore no preliminary injunction to Warner-Lambert.

AUDIENCE MEMBER: I just want to say I didn't intend to stump anybody there.

MR. COHEN: You stumped us both. Why did he find a serious issue, then? Because I thought the whole point was according to Floyd's test, you had to show that the pharmacist knew that he was going to be giving generic Pregabalin for the patented use.

Robin is looking as if he may be getting up. It may be to go to lunch rather than to answer a question. Isn't that right, Robin?

SIR JACOB: I think they've gone mad. If I play golf, like tee up, and there's a bunker over there and the odds are about 99 to 1 in favor that my ball will land in the bunker. But only a lawyer would say that I intended to put it in the bunker. And this whole question of intention, it rises in all sorts of things. In criminal law, say murder, you intended to kill or cause serious injury is, roughly speaking, the test. What happens if you do something where you didn't subjectively intend to do that, but objectively, that's very likely a consequence, the natural probable consequence of your action. That's not enough for murder.

At least in English law. When I was a kid we had a case called DPP and Smith and had a huge row about all that.

But I don't think it is good enough for commercial law. A guy who is selling a generic product, which he knows is going to be used 30 percent or whatever for the new use, ought to be taken to be intending the natural and consequent -- natural consequence of his use. I think that's what Floyd is roughly speaking he said.

It's what we said in Grimme. I can't say I can't help it. You know it's going to happen. I'll take the benefit of it. But that gives you the big problem of what happens when it's the 50/50 use, injunction or no injunction. Or an injunction you're going to raise your price. And that's why the more you think about it, the more you've got to focus on the payers and say listen, boys, you are paying for these new uses. You had better cough up the proper price for them.

So I think maybe the German route, in making these guys follow the money, as I say, and not the generic company.

MR. COHEN: Robin, sorry. It's obviously straightforward that the Grimme test was good. I'd forgotten it was one of yours. But it does say the ultimate intentional use.

SIR JACOB: We had a follow-up from Grimme -- which was KCI v Smith & Nephew.

HONORABLE KALDEN: I'm sorry. The answer to it, it's not intent in the sense of willfully or it -- it just means intent just the purpose, for the purpose of.

MR. COHEN: Yeah.

HONORABLE KALDEN: And yeah, I think it's the same test. It's a foreseeability that it's going to be used for the purpose of this indication. And that's ultimately done by the patient. And there's no reason to require that the doctor or the pharmacy should do -- should both consider the specific medicament made by the generic company, and the therapy that's going to be used for.

The ultimate end use is with the patient and he's taking the pill because he wants to be cured from this certain disease that this second medical use patent is all about. And that's my idea. And I think Floyd meant it that way as well.

MR. TELLEKSON: It's time to have lunch, which is presented outside here. And we can continue this discussion over lunch, but I want everybody to thank our esteemed panel.

[Applause.]

[Concluded at 12:35 p.m.]

PANEL VI
LEGISLATIVE INITIATIVES FOR ADDITIONAL PROTECTION AND GLOBAL HEALTH

Moderator:

Brian Cordery, *Bristows (London, UK)*.

Panelists:

Dr. Manisha Desai, *Eli Lilly and Co. (Indianapolis, IN, USA)*.

Adam Plich, *Teva Europe (Amsterdam, the Netherlands)*.

Dr. Allyn Taylor, *University of Washington School of Law (Seattle, WA, USA)*.

PROFESSOR TAKENAKA: The last two sessions are even more exciting, coming up with solutions for challenges identified as well internationally and domestically and things pending in Congress as well as different legislation as well as international agreement to be covered by this panel. So please come forward.

MR. CORDERY: So good afternoon everybody. My name is Brian Cordery, I'm with the Bristows office in London. Can I just say what a pleasure it is to be asked to participate in this event. And before I begin my very, very short introduction I do say I owe Rian an apology. We were both right but for different reasons. But it was refused by the court of appeal but Rian had me up against a wall at lunchtime explaining this issue and it's all been clarified. So thanks for that. Okay.

This isn't the first time in fact I've been at a conference on second medical use issues. With Sir Robin Jacobs in fact. I was proud to be part of the team in 2013 that organized a conference on second medical use issues back in London. Sir Robin engaged with that in his usual infectious enthusiasm, but it was really made possible by the joint sponsorship of both Novartis and Teva. And it was a great event. And since then, at least in Europe, we've seen second medical uses come more and more on to center stage.

In October 2013, I was in Venice for the judge's conference and at that conference the attendees were presented with a fictional second medical use patent and a skinny label generic medicine. The outcome of the debate was perhaps inevitable. The UK judges mostly felt the patent was invalid. The non-UK European judges mostly felt the patent was valid and everyone agreed that the issues of construction and relief were really, really tough, though none of the mega brains sitting around the table that day could offer a solution to the problem.

Last year in September I was in Toronto where Resolution 238 was passed by the AIPPI which deals with the situation where you have second medical use patents and skinny label use. I was actually very surprised by the level of unanimity from representatives of almost every country around the world that recognizes IP and they all agreed that second medical use patents were important and that cross label use should be preventable where the manufacturer knew or ought to know that its product was likely to be used for the patented application.

I note in passing that only the French raised serious objections to this, but then the French tend to do that when discussing matters on a pan European or global level.

So it's great to see how things have moved on in the last three years, both in terms of the case law and also the general awareness of the issues. But at the end of the day, case law and general awareness can only take us so far. This is because judges have a duty to apply the law and

at the end of the day some judges, and I do include Sir Robin Jacob here, they have been known to change the law a little bit, some fine tuning you might say, if they feel it's in the overarching interest of justice.

However, ultimately it is the legislators that will enact the will of the people and that's what this session is all about. So I'm going to very briefly introduce my distinguished panel speakers here. First we have Dr. Manisha Desai who is assistant general patent counsel of Ely Lilly in Indianapolis, and like many patent lawyers, Manisha began life actually on the coal face of her industry, spending almost a decade researching neuroscience before turning to the law.

Next along is Adam Plich who is also trained in science as a pharmacist but now works for Teva and looks after pricing and market access issues, things we haven't heard much about in the last few days. He deals with all aspects of Teva, the originator side, their generic side and the bio similar side. So that's Adam, and last but not least we have Professor Allyn Taylor who I think is home grown. You are resident here -- you practice here in the University of Washington?

DR. TAYLOR: At times.

MR. CORDERY: And Allyn pointed out, I'm not allowed to ask her any tricky IP questions; however, she is a leading authority on global health issues and the TPP and she's going to talk about that as we go on.

So we had a last minute change in running order so I'm going to try and get this right. We've decided that Adam is going to go first, then we'll hear the first bit of Manisha's talk. Then we're going to break while Allyn does her talk and then finally Manisha is going to close. I think that's the right order. So I'll sit down at this point and hand it over to Adam.

Thank you very much.

[Applause.]

MR. PLICH: Good afternoon to all of you and let me thank the organizers for the invitation. I've been already introduced by Brian. Let me highlight that I will be presenting more the payer, the pricing, the commercial perspective throughout my talk. Before I go on, let me state that what I'm going to say to you is primarily my own opinion.

Now, I already mentioned the perspective I will take in my talk. I want to outline the key message upfront -- and I think Sir Robin already has mentioned this on a few occasions -- which is that regardless of what is the IP or any other exclusivity protection a company will have managed to secure for the new use of established medicines, (and that's already questionable as I'm hearing throughout the conference.), the payers may not care too much on this. And we heard it earlier today about the insurers in the Netherlands or Germany that are actually setting up tenders without explicit considerations of these matters.

So let us step back a little bit. If I think about what is my responsibility, I always go back to the patient. I believe every patient, every person, should have or deserves an access to our medicines or healthcare solutions. But my job at the same time is to make sure that the prices make sense. Sometimes it may not really come together. What does it mean by the way that it makes sense? It needs to make sense for the payers for the health care systems. It needs to make sense for the patients in case they are paying, but quite honestly, it has to make sense for us, for the industry, for obvious reasons as well.

Now, throughout the day yesterday I had a few conversations with some of you and you asked me, well, you must have a very tough job? And how actually do you set the prices up? I'll tell you. Pricing has quite a lot to do with science. Why science? Because you actually need to understand what you are selling and you need to understand the value, and frankly, there's quite a lot of science in pricing itself. That may come as a surprise but it's quite a lot.

It's also an art because you need to put all of this together and you really don't know how it will all work out. But I like to point out to one important element, also the behavior, behavior in terms of how you negotiate, behavior in terms of how you price medicines from a societal point of view, behavior in terms of the discipline you have in the organization, in terms of not giving too much discounts and rebates. There's also competitive behavior. Behavior is important.

Now, the issue is that when it comes to the new uses of established molecules, this approach doesn't really work. Why doesn't it work? Because from the pricing and reimbursement legislation point of view - so it's not really even the payer's viewpoint, it's the legislation's viewpoint and I'm taking predominantly the European perspective here - the new uses of established medicines equal generics. And by the way, there's nothing wrong with generics, okay? Seriously. Again, generics are good. Use generics. But why is this the case?

So from the pricing legislation point of view, if a new medicine has the same ATC code as the old one, it's considered to be the same thing. If it has the same INN, it is the same thing. If it doesn't have a new active substance, it is the same thing. If it goes through what we call in Europe the hybrid regulatory procedure, it's the same thing.

And by the way, if you go to Poland, Germany, UK, you'll find different definitions in the pricing legislation of what "same" means or what "similar" means or what "equivalent" means. Sometimes they are very broad. Which means that if, according to the legislation, your new medicine that adds some value but it's using an established molecule is considered to be same, similar, equivalent depending on the jurisdictions, you are a generic.

And again, generics are good. But the problem with generics is, as Sir Robin mentioned yesterday, the cost of bisphosphonate is roughly around \$20 a year. And by the way, in some countries it's a little bit less than this. We are in Seattle, where Starbucks come from, so for \$20 per year you can get around six cups of coffee. How many of you have had six cups of coffee last month?

And by the way, this is an annual treatment of the therapy that prevents fractures, okay? Just to put it in perspective. But if Teva or Novartis or any other company decides to invest into the new treatment, and let's say we want to innovate around bisphosphonate, and we heard yesterday we can do quite a lot of stuff around bisphosphonate, the generic price is not going to work. Simply it's not going to work. It may work if with a generic you have a massive volume, if there is a minimila investments in R&D, the company will be selling the product for other price, but it's not going to work if you want to put a couple hundred millions or one billion dollars, depending on how complex it is.

How does it work? For those of you that may not be familiar, I just took five major European countries, France, Germany, Italy, Spain, UK, In these countries, the legislation enables or enforces that generics need to have a certain level of price and it's mandatory like in France, Spain or Italy, or it enables quite a fierce price competition in terms of the rebates the pharmacist tenders, claw backs and so on in Germany and the UK.

Now, the issue is also in the U.S. It's not necessarily regulated in the same manner, but when I talk to my U.S. colleagues, they also find that such situations may be difficult. And this is actually an article that was published last year by a number of different people from the U.S. about how to overcome the obstacles to repurposing old molecules for neurodegenerative diseases. And what they said is that if generic versions are available, the challenges are even greater since payers can promote a generic switch, even if branded drugs have a new indication.

So a number of quite notable individuals are stating this in the consensus paper. They also said that it definitely discourages companies from investing in clinical trials to prove drug efficacy.

Now, they then go on and they say payers are unlikely to cover a new formulation, altered dose, route of administration or a combination therapy over existing approved drugs without demonstration of clear clinical benefit at a reasonable cost.

And I want to highlight this because let's say you, Teva or other company innovates around the old molecule. What we really need to show is that we add value. What does it mean? We need to have a clinical study that is powered to show superiority. And for those of you who are not close to the R&D world, superiority study is risky, it's really costly. The simple bioequivalence or non-inferiority studies are much cheaper to do. And if we want to get a high price we actually need to show it in a clinical trial. If we don't have a clinical trial, we may have fantastic IP and exclusivity rights, but it's not going to work.

So naturally we struggle with it. We struggle because of the cost and risk of development that such medicines with the new uses of established molecules are roughly hundreds times more than generic. I actually am basing it on a specific case that we have in Teva that I use around negotiations.

In addition, We haven't mentioned it too much but actually it is a much higher regulatory uncertainty with developing the medicines with the new uses of old molecules than with generics. And also there is higher cost in terms of the post-approval safety studies (PASS) or other regulatory obligations that are agreed as part of the risk assessment plan.

Some other things. Up front investments in manufacturing can be big because if you want to innovate, you may have an interesting technology but that technology can be very costly to set up. We talk about hundred of millions in just manufacturing plants sometimes. And believe me, there is a case that I can definitely refer to. Cost of goods are much higher than typical generics and the commercial investments are much higher than with typical generics. So the whole comparison with generics simply doesn't make sense.

Now, there's one other thing. You may wonder what you are looking at. That's my daily life. I mean seriously that's what I do. So let me take you through this - what does it mean? So this is what is called international price referecing matrix. To put it in the simplest possible language, One government doesn't want to pay more than the other government. That's basically the rule in Europe. And this table describes how it works.

So if you look at the vertical columns, these are the countries that are referring those countries when they set the price. So what does it mean? If I'm launching the product in Germany and if I happen to go through what is called the AMNOG procedure, at some point the German negotiator will come to me and say, Hey, what are your prices in 15 other European countries? And just to put it into perspective, in the German basket, I have Greece, Slovakia and Czech Republic – nations that significantly poorer than Germany.

But what does it mean? I'm launching the product in Germany. That's my No. 1 market. And I don't really want the price in Germany to be negatively influenced by the price in let's say Czech Republic or Slovakia or Greece. I will never be paid by the way in Greece.

Now, seriously, no. So what does it mean? I'm not launching the products in those countries, and believe me, this is the kind of decisions, I don't want to say, I make every week because I'm trying to get the product everywhere, but once in a while, every quarter we're not launching a product somewhere because of this topic. And that topic is even bigger for the news of established medicines because if even one country favors through the legislation that sort of higher pricing that recognize the value of the new uses of old molecules, it gives this pricing incentive, then I will prioritize those countries first and I may unfortunately neglect other countries.

You may think it's unethical, but if I do it in the other countries then I lost the whole business in the countries with higher prices.

So what are the consequences? I think we talked about this, but in the long run, obviously we may not have all those medicines in all countries. The companies will either decide not to invest anymore or they may decide to launch only in countries that provide pricing incentives

Why is it a case? Well, here is a paper that recently was published that addresses this point. I contributed to it and it's about innovating about inhalers in asthma and COPD. In general, we have great molecules, but we have poor inhalers hence the need to innovate around the inhalers. And what this panel concluded is that patients will only be able to benefit from innovation in inhaler devices if the pharmaceutical manufacturers have sufficient incentives to invest in such innovations. What they say then is that the lack of recognition of innovation in inhaler devices which deliver off patent molecules will at best deprive the patients access to the medicines – and can lead to inequalities across countries – while at worst it can limit the financial incentives for us to actually put the money into the development of these medicines and bring them to market altogether.

Now, coming back to this paper which I mentioned to you earlier, it talks about something very interesting. The authors say if a repurposed generic drug lower payer costs significantly, as there will be an effective low cost treatment available where previously there were none, generally speaking, in such situations, there may be a portion to actually work in the payers in some sort of partnerships to, you know, to put the system in place to recognize innovation in the uses of all molecules.

I refer to the example that we had yesterday, the Alzheimer's. That's exactly the case. This company innovates around a system, but if they would be able to show that they are lowering the treatment cost of Alzheimer's, that actually can work very well for them and for the payers as well and there may be incentives for them to do.

So my call to action. I think generally speaking the

What are the potential solutions? What are the potential legislative solutions? Well, I think that yesterday it was mentioned on a couple occasions that HTA, Health Technology Assessment, may be one of the ways to address that. What's the health technology assessment? It's basically a way to systematically assess the evidence and the value of the medicines compared to what is currently being used.

The big issue is, however, and this is what is described in the table here on the right-hand side, is that for the medicines that come with the old established molecules, in many countries the route to even go through HTA is blocked. From the pure legislation point of view these medicines are considered generics. Because they're considered generics they cannot go to HTA. That's the case with AMNOG process in Germany. That's the case in Poland.

Okay. So that's the first thing to fix. It's very easy things to fix, just let's open up the legislation so that if the company wants to go through HTA, we can have a possibility to do this. And one of the ways to address that potentially could be to, within the agenda of EuneHTA at the European level. There and there was a discussion yesterday on the topic: to bring those medicines into the agenda as well not just the originators

I think we've had many interactions about the new indications. One of the solutions is just to create a system where you can differentiate the price between the indications, but you cannot forget about pharmacy substitution systems as we heard it very clearly in the morning.

Procurement. In Germany, when you have a tender, and that's clearly stated here, the only thing that matters is price, that's it. So if you're a generic, and these kind of medicines will be considered generics, the only thing that will matter in the tender will be the price.

And finally, I think there's another level that we can engage in, it's the World Health Organization (WHO). Why WHO? Because they are in charge of the fundamental system of classification of medicines. They're in charge of granting INNs, granting ATC codes and defining the daily defined doses (DDDs). And I'm not going to go through this in detail what it all means, but the bottom line is, if WHO is open to differentiate at that level between the new uses of the medicines and the old ones, then this creates a very strong foundation for all the health care systems to follow because all the health care systems have signed up to it.

Now, I also think there is some responsibility we need to put on ourselves. I think, first of all, if we innovate around those medicines, I think we need to bring value to the patients, because otherwise, if we talk about a very small incremental innovation, it might not necessarily be the solution. Other thing is to generate evidence. One of the general managers at Teva always say to me: if you can't demonstrate it, shy away from it. And that's an important component as well.

I think the other point is that we may litigate with the payers in case there is a disagreement about the price but I would prefer to work with payers as customers and partners. It's difficult sometimes, but at the end of the day that is my vision, so I think as the industry we need to open up much more for those kind of partnerships. At the end of the day, the payer's mission is to help the society the greatest public or population health while managing budget so to speak. They have the inherent mission of public health. Even if they are the private payers, they have the obligation to follow.

And I think it's something we can tap into as well. It's just not always about the costs, even if that's the type of thing you always hear for 95 percent of the time.

I think the other thing is about pricing. We should price the medicines with the new uses of established molecules responsibly. We should reflect the value of those products in their prices.

But I have something to say to you actually. I would love to see this conference next year with payers here.

SIR JACOB: We tried to get them.

MR. PLICH: Maybe we should work together on that. I think we need to bring them here because they are the only ones that can change the system. And it seems, based on the judge's ruling of the pregabalin case that we saw earlier, that that's also what was recommended because, frankly, we as a group are not going to be able to sort it out by ourselves. Thank you.

[Applause.]

DR. DESAI: Thank you. I'd like to thank the organizers very much for the opportunity to speak with all of you today. As you heard, Allyn and I are going to do a little bit of a public/private partnership and divide our talk. I'd like to start first with development, drug development and incentives in the U.S. and then Allyn and I will both address the Trans-Pacific Partnership.

So you can't have an industry person talk about drug development without seeing some form of this slide. I know you've seen it a lot so I won't cover it in much detail. It's either a funnel. It's a rocket ship. Whatever it is. But the point that I want to make with it, I guess there are two to three points that I want to make and that is, you've heard that we filed the patents early and the longer it takes to get to FDA approval, the shorter the remaining patent term.

We also have in the U.S. regulatory data protection and there are different coverages for small molecules versus biologics, five versus 12 years, but those overlap with the patent period. And just to make it a little more personal, I will say that I started in the patent division 16 years

ago and I started by drafting patent applications. And with regard to how difficult it is, nothing I ever wrote became anything so all the -- everything has failed basically.

So you have heard and you will hear some more that there's kind of a perverse reality about the patent system and that is that we do file our applications years before the product receives approval. And of course, if medicine is truly innovative, it's going to take longer to go through the clinical trials, and of course, longer development means shorter patent term. And it's this variability in the patent term that creates a disincentive to really work on and innovate and develop the most novel medicines and innovative medicines.

And so we have what we call a modern solution. In the U.S. there was an initiative -- legislative initiative called the MODDERN Cures Act, and it was actually developed by a coalition of patient advocacy groups, the National Health Council, and it created a concept of when a therapy is dormant, the act provides mechanisms of a fixed incentive -- or a fixed period of protection to provide an incentive to create that and to develop that therapy.

So the idea of the MODDERN Cures Act was a fixed regulatory data protection, a period of 15 years, during which no generic or bio similar applicant can obtain approval of a product by relying on the sponsor's data. And the designation of dormant therapy is something that the FDA would grant, a sponsor would request it, and when a dormant therapy is listed as such, the sponsor would have to provide a list of all patents and patent applications that would protect that medicine.

And the idea of the dormant therapy is not only the fixed period of 15 years of data protection, but also the extension of any existing patent rights to the end of that 15 years, but in addition, the waiver of any patent rights beyond that 15 years. So what medicines would qualify? This is an FDA categorization. An unmet medical need would be something that is serious or life-threatening and for which there is no available therapy, or in the alternative, there are several conditions that could also qualify. And the critics of this proposed bill have argued that 15 years is too long, but in reality, the U.S. Hatch-Waxman system is capped at 14 years. There is a period of six-month potential pediatric exclusivity and there is a period of 180-day or six-month exclusivity for the single first generic. So a medicine with a strong patent protection gets about 15 years anyway.

Some have criticized it as it would allow too many products to qualify, and actually it's a standard that the FDA uses to define what is an unmet medical need. So it would be, I think currently or recently it's been about 40 percent of FDA approved medicines.

And finally, the idea that there is potential for abuse, and the reality again here is that the patent owner is giving up any rights to any patent protection beyond the 15 years so the criticism of evergreening actually cannot apply.

But as with all good things, the House, the U.S. House carved out the MODDERN Cures provision from the 21st Century Cures Act which was passed in July of this year, and a corresponding bill in the Senate was introduced in 2014 but not passed and it was not reintroduced yet in the current congress.

So actually, that's my breaking point and to be continued later.

[Applause.]

DR. TAYLOR: Thanks so much. This is such a pleasure to be here this afternoon. I want to thank the organizers, especially Toshiko and Rupert for inviting me to join his panel, and I have to reiterate again because it makes me so nervous. Unlike others on this panel and in this room, I am not an intellectual property attorney so no tricky questions. And consequently, I really learned a lot in the last day and a half, not only by a series of really marvelous presentations, but also with

the number of side dialogs, with generous and highly patient patent attorneys, and you know who you are and I appreciate our conversations.

My expertise is in international law and global health policy and I'm going to try and bring a bit of that background on training to look at some of recent legal developments surrounding new uses for old medicines, particularly with the Trans-Pacific Partnership Agreement and then Manisha will be coming back with the industry perspective.

As we've been discussing over the course of the last two days, finding the balance between health trade and IP policies to sustain innovation and ensure widespread access to life-saving technologies is one of the primary public health policy challenges of our time and as Dick Wilder so reminded us yesterday, we've long been out of balance. In the -- historically, medical innovation has failed to address major diseases that are endemic to most countries. According to Medecins Sans Frontieres, MSF, only four percent of new drugs and vaccines that have been developed between 2000 and 2011 were for neglected diseases.

Now, whether it's called drug repositioning, reprogramming, repurposing or reinventing, the process of reusing these old medicines is beginning to change the picture for neglected diseases. As we heard yesterday, public and private product development partnerships were springing up to repurpose drugs for neglected diseases. And in addition to the important work being done by Gates, there are a number of other public/private partnerships such as the Drugs for Neglected Diseases Initiative and the Medicines for Malaria Venture who all viewed drug repurposing as a critical avenue for providing cost effective and timely access to drugs to patients in developing countries.

I think the key question in this realm is how to incentivize pharma to donate compounds to participate in these partnerships in a way that ensures widespread access to essential medicines at affordable prices.

Another critical issue is the tension between public and private sector interests in drug repurposing. I'm sure Jerry McLaughlin, who's not looking, did not expect to see himself on my slide but he really struck me what he said yesterday. I think he so well described yesterday that the tension is due in part to some public interest bias against repurposed drugs. And I think it is really fair to say that advocates tend to view drug repurposing as mere illegitimate attempts to extend the patent life of a drug without real innovation. But unfortunately this has been bolstered by the words and actions at times of the industry itself. Indeed, the literature is replete with industry reference to patent clips and drug tweaking.

And opponents of evergreening, including organizations such as MSF and Oxfam, point to exactly these types of statements and the practice of extending patents to minor or trivial modifications that do not advance public health as the reason why new patents should not be granted for old drugs.

Now, I think Jerry is absolutely right in pointing out that not all repurposed drugs are low level patents. Indeed, many involve substantial investment in innovation. But we also need to recognize that there are bad players. And ultimately there are important conflicts between the public and private sector interests, particularly with respect to repurposed medicines that can have wide-ranging impacts for global public health.

So what's the global legal framework? We know that the multilateral legal IP framework provides the context and the general guiding legal principles then for the operation of national IP systems, including the framework for drug repurposing. The WTO TRIPs agreement has significant implications of course on the application of IP to medicines, but is notably silent on new uses.

Now, since the adoption of TRIPs, patents on new uses has been extensively debated and there's no commonly accepted international practice. And ultimately, the issue of patentability is not just a technical decision, but I think it's above all a political decision linked in a way in which a country which is to interpret and apply the patentability criteria in order to promote and protect economic social and technological developments.

Now, some developing countries, as I'm sure you're all well aware, have resisted the trend for packeting new uses. India, countries of the Andean community including Peru, Bolivia, Venezuela, Columbia, Ecuador, among others, expressly exclude new uses. Other countries such as Brazil do not have express inclusions or exclusions, but have at times denied second use patents as not being novel or inventive enough.

So although the TRIPs agreement leaves members some flexibility on the patentability of second uses, I think the rule may be shifting with the recent adoption of the Trans-Pacific Partnership Agreement. As you know, the TPP is a massive trade deal that covers 12 countries constituting 40 percent of the world market. Negotiations of the TPP concluded in October. The agreement was tightly held -- though many of you in this room may have seen it. I'd be interested to know that -- during the negotiations and the draft was only released to the public less than a month ago. And the agreement is absolutely enormous. The chapter on intellectual property alone is 74 pages and it covers numerous areas.

Now, during the negotiations, public interest and public health groups, including some UN agencies, voiced concern over the TRIPs plus provisions in the Trans-Pacific Partnership Agreement. The TRIPs plus provisions in previous trade deals, as you know typically have imposed a higher level of protection for intellectual property rights than is required under TRIPs, and advocates argue that the so-called TRIPs plus provisions limit or undermine the capacity of developing countries to legislate and use TRIPs flexibility to ensure access to medicines. And it has been argued that the TRIPs plus provisions in the TPP could impose obligations on developing countries that go far beyond any other trade agreement.

Now, public interest groups are particularly concerned about the TPP, because besides the fact that it's a massive agreement in and of itself covering 40 percent of the world market, it was designed as a platform agreement that can be acceded to by other countries. The TPP has also been touted as a new gold standard for future trade deals and is expected to set the precedent for similar provisions to be included in these future agreements.

Now, I think at this point the full health implications of the TPP are difficult and impossible to judge for a number of reasons. Again, the provisions were markedly complex. The agreement was just released. It is also important to know that the draft that we have seen and that is available has not been through the final legal scrub so the provisions could change. And also it's important to note that there's considerable question about when or whether the TPP is ever going to enter into force. The text requires the agreement will enter into force when at least six the signatories have completed applicable ratification procedures, provided that these six countries together account for at least 85 percent of the combined gross domestic product of the signatory. And what that means in short is that the TPP will not go into force until when and whether the United States decides to join.

So what are the provisions of the TPP? And Manisha is going to have a lot more to say about this. Like TRIPs, TPP provides that a party shall make patents available for any invention that meets those three standard criteria, being new or novel, involving an inventive step, and being industrially applicable. And subject to certain exclusions article 1837, which is the key provision for us, explicitly requires parties provide patents for new uses, new forms and new methods of use.

Now, there are other provisions also to create the potential for extending patent terms for new uses, and these are going to be more thoroughly discussed by Manisha, including article 1850 which provides three years of data exclusivity for new uses of old medicines and Article 1846 which mandates adjustments in patent terms for patent office delays.

Now, the debate around these articles has been stirring for some time. Advocates argue that these new use and other provisions will extend patent terms and limit the capacity of their governments to use TRIPs flexibility such as compulsory licensing to protect public health. But proponents of the TPP argue to the contrary, that the concerns of the public health community are simply overwhelmed and that indeed this agreement allows ample flexibility for states to protect public health.

And it does so for several reasons: First of all, like TRIPs, the TPP does not precisely define the criteria patentability, right, there's three provisions. So it gives some countries some flexibility, as we like to say in international law, "wiggle room," right, to interpret these provisions.

Second, the provision includes specific -- agreement includes specific provisions on the authority of countries to protect public health, including and particularly this provision Article 18.6. There are also other provisions that reach out to public health including Article 1841 that explicitly affirms the right of countries to use TRIPs flexibilities.

Now, although the TPP includes a specific public health provision and others, I think there are other provisions in this agreement that are likely to have a chilling effect on the use of the public health exceptions and TRIPs with respect to not only second use, but first use patents. And I want to just briefly describe those. I don't have much time. And what I'm particularly concerned about are the enforcement provisions of the TPP.

Indeed, in some respects, the enforcement provisions of this agreement and the secretive manner of its negotiations are tremendously reminiscent of ACTA. You all may remember that failed anti-counterfeiting trade agreement that was assigned to be an enforcement agreement for TRIPs. Well, I think the TPP has a lot of provisions that were just sort of the pulled out from ACTA. First of all, the TPP mandates that rights holder have access to civil judicial procedures, including the possibility of injunctive relief. Notably, the agreement also requires that state law provides a presumption of patent validity and civil and administrative enforcement proceedings. And what this means is likely increase of probability of interim measures like injunction. There are a number of other important provisions here. Article 1874 also includes the potential for debilitating financial damages based upon any legitimate measure of value that the rights holder submits, including suggestive retail price. And the concern does not stop there because the TPP also provides that judicial authorities shall have the right to impose court costs and expert and attorneys' fees.

The provisions on discovery are also extensive and potentially chilling, including the right to access information about persons that -- allegedly involved in the infringement, the means of production and channels of distribution. And I think finally and most controversially, I just want to say a few words about Chapter 9 of the TPP which creates an investor state dispute mechanism.

Now, this investor state dispute mechanism could potentially empower foreign companies to sue state parties for hundreds of millions of dollars in damages in the claim that their rights have somehow been undermined. Notably, such provisions have been included in trade agreements before of course, but the scale of the TPP substantially increases the likelihood of more of the number of such challenges.

I think also of concern is that the TPP does not include any meaningful provision protecting states from these investor claims when they introduce regulatory measures to protect public health

or other policy interest. Now, Article 9.15 of the TPP has been touted as the public health exception for TPP but it merely provides that states can introduce such regulatory measures to protect public health and other public interests that are otherwise consistent with the agreement. That renders a provision essentially legally meaningless.

Now, notably, firms have used provisions like these investor state dispute provisions and bilateral trade agreements to challenge a range of laws, and most recently they were used to challenge public health laws in Australia in the top context of tobacco control. The tobacco control community is so strong at the global level at this point that they were able to carve out an exception in the TPP. So this investor state dispute resolution procedure does not apply in the context of state measures on tobacco control.

Now, in my view it doesn't make health policy sense that one public health concern gets carved out of the TPP but not others. Notably, the TPP has a strong state-to-state dispute resolution mechanism, including the possibility of trade measures being imposed. I believe that the private sector shouldn't have the authority to bring sovereign governments to arbitration proceedings for decisions to protect the public health, and we need to recognize that the mere potential for arbitration, as well as the potential negative outcome may indeed induce a regulatory in Chilean countries, especially in low income countries that do not have the resources to battle investors.

So in conclusion, increasing number of bilateral and regional trade agreements, including the TPP, highlights need to analyze these agreements very carefully from a public health and economics perspective. And this was just the beginning. The agreement says it's not necessarily the last word. There is today limited analysis of the impact of intellectual property laws in most countries and although the fate of the TPP is uncertain, I think the negotiations themselves have helped us to refocus attention on issues surrounding access and innovation and is contributing to the discourse that we're having here on alternative mechanisms for incentivizing innovation to protect public health. Thank you.

[Applause.]

DR. DESAI: I've missed you all. Okay. So the point I want to make with this slide, you know, I won't go through the numbers you've heard many times, the pharmaceutical industry, you know, spent over \$50 billion on research and development last year, and actually this number is from pharma so that number only reflects pharma member companies. It does not include other biopharmaceutical companies that are not members of pharma.

In the U.S., Americans are very concerned about health care costs. We hear it in the news all the time, and I think a large part of the reason is that although prescription drugs remain at about 10 percent of health care costs, payers, the actual patients, are paying about 40 percent out of pocket. And meanwhile developing countries are a growth opportunity and some have said the emerging markets will represent about 42 percent of the global pharmaceutical market by 2019.

So the question is: Who's going to pay for all these medicines? And I have a bad habit, when I'm on airplanes and I talk to the person next to me, and the gentleman next to me on the way to Seattle gave me a Wall Street Journal which had on the title page the fact that Americans are subsidizing the health care costs for the rest of the world. So when I look at the TPP, I look at it may be slightly differently than what you've just heard.

So in the U.S., the ability to negotiate the Trans-Pacific Partnership is dependent on the ability of the administration to negotiate and then not have everything renegotiated by the Congress, and that authority came from the Congressional Bipartisan -- excuse me -- which is a rare word in the U.S., Bipartisan Congressional Trade Priorities and Accountability Act, or often referred to as TPA. And the TPA sets goals for what Congress, what legislators hope to achieve

with negotiation of a bilateral or multilateral agreement. And in the IP section, it includes the provisions of the trade agreement -- of any trade agreement that is entered into by the U.S. should reflect a standard of protection similar to what is found in U.S. law. And second, that preventing or eliminating discrimination with respect to matters affecting availability, acquisition, scope, maintenance or enforcement of IP rights. And so the question is: Were these goals achieved?

One of the things that the pharmaceutical industry was paying very close attention to, as I'm sure you've heard and are aware of, is the data -- regulatory data protection provisions. In the U.S., as I've showed in my first set of slides, we have five years' regulatory data protection for small molecules and 12 years for biologics. And although the TPP does say there is five years of regulatory data protection from the data marketing, there were several annexes that I don't think that we weren't aware of when the announcement was made in October, but have had a chance to see when the text was released in November. And essentially, a lot of that protection is eviscerated by various annexes and side letters.

So as an example, Peru has a free trade agreement with the U.S. that was signed in 2010 I believe, and it includes regulatory data protection for five years but it says that if Peru approves the drug in less than six months after -- for example, if the innovator relies on data that we used in the U.S. and Peru approves the drug in less than six months, the data protection period is based off the first approval anywhere in the world.

So it really doesn't equal five years. It's more like three and a half. And although they say they have to approve in six months, we had an instance in Peru where the agency asked for additional data and decided to stop their six-month clock, so even though it took them longer than six months to approve, we still only got five years from the first date of approval. And that exception remains in TPP. And of course with biologics, in the U.S. we have 12 years of data protection, and as we -- as I believe you know, that is not reflected in TPP.

So another provision that we -- you heard earlier about the Hatch-Waxman law in the U.S. and what that allows the innovator and the generic to do is to resolve any patent disputes before a generic is launched and before we get into horrible damages as Allyn alluded to. So the TPP includes provisions on notice to the patent holder and early a resolution mechanism, but also included side letters that basically either exempt or weakened what various countries had already agreed to.

So again, Chile and the U.S. entered into a free trade agreement in 2004 and it included these early resolution mechanisms, but as of 2015 Chile had now passed those or put those provisions into their law, and now with TPP, they -- the provisions are weaker and they basically did not -- have 11 years of not abiding by the original free trade agreement.

So to go back to the first part of my talk, I will just say that Lilly was a strong supporter of the MODERN Cures Act and a period of fixed exclusivity and -- as a mechanism to ensure greater certainty and encourage development of drugs for unmet medical needs. And so we look at these things and we believe that there are ways to legislate innovation or to incentivize innovation but unfortunately they're still theory at this point. Thank you.

[Applause.]

MR. CORDERY: Thank you very much indeed. I'll open the questions to the floor in just a few seconds. Got a couple of questions of my own. My first one is to Allyn and it's about the law of obviousness in Sweden, Allyn.

DR. TAYLOR: No, no, no.

MR. CORDERY: I have three questions for you, Allyn, they're all wrapped up in one. Will the TPP be signed? Does it depend on who is in the White House and will that person be called Hillary or Donald?

DR. TAYLOR: Well, I think it was signed, right?

MR. CORDERY: Will it come into force then?

DR. TAYLOR: Will it come into force? I think that's a political question. I don't think it's going to come into force during this administration. This is my own view of the political, you know, political wins. I don't think that this is -- even though I think it's a benefit to the business community and the public, I don't think they're going to want to support this during this administration. I think it might take -- if it enters into force I think it's going to take a couple of years. What do you think?

DR. DESAI: So for once I'm going to speak on my own behalf and not my company's behalf. I will say that our CEO, two days after it was announced, publicly did say that something is better than nothing. He was disappointed but that any improvement in patent law is better than nothing. And now that the text has been released I don't know what our CEO and I don't know what our company thinks, but a lot of the things that I thought would improve in the countries that I have managed, I see as being really not -- no better enforcement mechanism, no real improvement in data protection, which is really the certainty that we would all like to see, even though that would put me as a patent litigator out of business.

But as a patient and a payer of medicines, it would certainly be the kind of certainty that ensures innovation. So do I think it will pass? I think that the Senate has expressed a lot of reservation so Senator Hatch has already criticized it as, again, not meeting the goals of the TPA that Congress passed to allow the administration to negotiate the TPP. So I'm actually kind of skeptical.

MR. CORDERY: Thank you much. Allyn, did you want to make an additional point on that?

DR. TAYLOR: Who's going to be president?

MR. CORDERY: Sorry.

DR. TAYLOR: I think one of the sort of interesting questions is how it will be used as a model agreement for future agreements. So, you know, there are these two ideas, one is that other states with the agreement of all the parties can accede, assuming it enters into force, or it will be a model to negotiate other agreements. And I think if I would happen to access -- and I'm not a trade lawyer either, I'm a global health lawyer, the fact that this agreement was negotiated in such a secretive way, right, where techs apparently like to our Congress, they were allowed to see the agreement where we're not allowed to take notes or keep copies of it, right?

So I can imagine like trying to negotiate an agreement with Europe. I don't think the Europeans would tolerate this. I mean they would say this is why ACTA failed. So if it's going to be a model it's not going to be by acceding to this agreement but that there will be separate agreements that include provisions. And I do take exception even with Manisha because I think the investors say the dispute resolution procedure is a huge improvement for the business perspective. So I think other, you know, I think companies would be quite interested in advancing the agreements that include that provision.

DR. DESAI: So you promised you wouldn't bring it up but I will.

DR. TAYLOR: I'm not going to bring it up. We're polite.

DR. DESAI: So those provisions have been in free trade agreements and they have not been -- although there are individual cases, they have not been used every time that someone's

patent rights are weakened or taken away. I mean, you know, if we want to talk about delays or lack of patenting, as you yourself mentioned, there are so many countries that I manage that we can't get second medical use patents. You mentioned Latin America, the Andean pact countries. In Brazil we file applications that are still pending 12 years after they were filed, still unexamined by the patent office, and I've actually had to tell our Brazilian affiliate that they are launching a new drug and even though we filed the application they don't have any patent protection.

So these are, you know, these are not member countries of -- or at least Brazil was not part of the TPP, but these are real issues that we are trying to have addressed by these free trade agreements.

MR. CORDERY: You talked about transparency and I think we all agree that it's terribly important and it sounds like it was a dreadful business by not being allowed to read something and not take notes or something. Here is the question I want to ask Manisha. I mean if in preparing for this presentation this afternoon and moderating it, I looked at what has been happening just in the UK in the last 12 months. There's an extraordinary thing, there's a thing called the off-patent drug bill was proposed, and the idea was that for -- basically where there was promise in a new indication, the secretary of state in the UK could apply for marketing authorization so that that medicine was licensed rather than being used off-license so to speak. And that bill was actually thrown out using a process called filibustering. And filibustering, do you know what that is?

DR. DESAI: I thought only we had that.

MR. CORDERY: Okay. So filibustering you have in the U.S. Okay, the guy was supposed to get a conservative minister called Alistair Burt, essentially used up all the time dedicated to discussing the proposed bill by just going on and on and on and timed out and the thing doesn't happen, which seems to me extraordinarily like cross-party support. So my question is? Are things any better on your side of the pond? And I'm hearing the answer no but do elaborate.

DR. DESAI: Just turn on the TV and you'll know the answer. You know, we were really disappointed with, as I mentioned, the MODDERN Cures provision. We thought that it made a lot of sense. It was really aimed at just incentivizing medicines that would otherwise not be developed. And it was disappointing that not only did it not -- it got carved out of the House bill so I think, you know, the opportunity to bring that back now is very -- actually very small.

In the Senate, again, it got killed by -- it was very much not a bipartisan bill. And I don't - - I had in my slides, not reintroduced, and a colleague of mine who is so much more optimistic than I said, please put "not yet reintroduced." But the reality is I don't see it happening, especially in an election year.

MR. CORDERY: Okay. Time is passing so let me open up the floor and ask if there's any questions for any of our speakers this afternoon?

AUDIENCE MEMBER: So from what you described about MODDERN, I didn't see how it would help new uses of old medicines. It in fact seemed like it would inhibit that by preventing patenting or the benefit of patents if there was another substantial new use. For Allyn, I'm just curious: Why does anybody care about these small increments that are patented when they're -- if they're not necessary for a generic version of the drug? Why would payers pay for it? Why would patients care about it? And why are people worried about this incremental innovation that doesn't make a difference? Because you could still have now that withdrawal can be only based on safety issues and we can no longer orange book list a patent five minutes before and get another 30-month stay, so who cares about these incremental innovations? They may be important and we don't know when we file the patent application. Why should they be denied?

DR. TAYLOR: I will say while they're negotiating I'm going to answer the question. I think you make an important point. First of all, there's a lot of misunderstanding about the way the law works in this area, right? And there's a lot of rhetoric that evergreening covers the compound as well as the new use. So I think there's a certain degree of misunderstanding and that's why there is a lot of dremity [sic] around it.

I also think that, again, not being a pharma person or an IP, there is concern that may be legitimate that there may be minor tweaking that's going to affect the usability of that new compound. And perhaps somebody else could speak more directly to that.

DR. DESAI: Well, I think I was confused who you were asking questions to, but I will at least take my part of the question you asked as for new uses and I'll do it somewhat anecdotally. So the idea is if you have something that does not have extensive patent life, and I have been in meetings where someone will ask, Well, when does this patent expire on some compound that was in development but then got pulled or got put in what we call the parking lot, just got put to the side for a little while, someone is interested again, wants to look at it for a new indication. Asks me what the remaining patent -- or what's the patent expiration date. If it's three years, five years, that's really not even enough time to develop it.

And I don't -- I don't know what happens or what decisions got made, but I do know that I didn't get a new project. I mean that didn't become something I was working on. So the idea is not just new uses of old medicines, but the ability to develop a drug that might otherwise not be developed because of other concerns. And with regard to --

AUDIENCE MEMBER: That was the question I had for you.

DR. TAYLOR: Actually the final reason, I mean there's concerns that you could have minor changes, minor tweaking that can have profound implications for public health, but the public community will not have access to it. And I want -- I don't want to bring it up Jerry, but let's talk about the antithesis of the example he gave us, right? Which is the development of new use or a new formulation, right, new dosing of an existing compound for Alzheimer's, which -- and he showed us the global burden of disease.

So people in the public health community want to know how are we going to get access to that medicine to the millions of people around the globe who need it and when you have -- and I don't want to use his example, a drug that is being repurposed with new dosing at minor cost, minor innovation? You know, I think this is exactly where there's a tension between the public sector interest and the private sector interest.

AUDIENCE MEMBER: Then it comes down to pricing. We in pharma ask for a price. Guess what? We don't always get it. In fact, we almost never get it.

DR. TAYLOR: Exactly right. We had an extensive discussion about that, you know, in the context of this innovation, so absolutely.

DR. DESAI: Can I --

MR. CORDERY: Please, briefly.

DR. DESAI: So the point I did want to make about the 15 years and subsequent uses for that compound, I've been in meetings and I have witnessed that, you know, when a new drug launches in the U.S., because of the Hatch-Waxman system, it's going to be challenged in four years, five years. And so when the team is trying to make decisions about are we going to try to develop this or a new indication, are we going to look for a cancer drug, new cancers that it could treat, they feel like they're in limbo. Well, are we going to have exclusivity to be able to invest in that or are we not? We don't know until we go through the patent case.

So the idea again of MODDERN Cures is you will get 15 years and you know you get 15 years, and in that 15 years, you have the -- at least the certainty that you are recouping the investment that you've made and have the ability to invest more.

AUDIENCE MEMBER: Thank you.

MR. CORDERY: Thank you. The reason I haven't had the television on, Manisha, in the last couple of days is because I've been absorbed in this very interesting book and I've visited all the good bookstores and there are only four now left on Amazon. But actually, one of the highlights so far of what I've read in here is Sir Robin speaks to the public sector inquiring report in Brussels which was given in 2008 -- was it that long ago? My goodness.

And he talks in there about quotes from the Pied Piper of Hamelin about how everyone wants to pay a master price for something and then they get it and then they say, Oh, we possibly can't pay that much for it. And the fact that pharmaceuticals cost, some pharmaceuticals cost quite a small amount of money to actually manufacture, but in reality all the money goes into the investment both for that medicine and for all the medicines that didn't make it along the way of course and everyone in this room well understands that.

But the problem I have is that we all in this room all understand that but the people who read the daily newspapers in the United Kingdom, and I'm sure the same is true across the world, did not get it, and yet they're quite happy to pay for expensive cosmetics or expensive clothing which costs next to nothing to make it.

So my final question goes to Adam, and Adam, you negotiate prices for originators and for generics, yes? It's part of your job, the metrics which make me glad I've got my job and not yours. Do you have a set formula if someone, a layperson asks you, you know, why do medicines cost so much? Adam, you deal with this. Why do they cost so much? What's your answer to the world on that one?

MR. PLICH: So first of all, I encourage everybody to work in pricing. I think it's very interesting. In reality I can tell you I had the pleasure to work with a fantastic group of lawyers at Teva, and you will probably hear from one of them in the next panel, and the legal world is not too far from the market access world because we also need to present the case. We are presenting the case. We are also the judges, which is usually the payers or bureaucrats, but it's similar in my model. Anyway, to your question, first of all, I don't think that the medicines are that terribly expensive to start with. Why is that the case? If you look at the proportion of spending in medicines in the majority of the European or global countries, they constitute a rather small proportion of all the costs. I think that's the other part of the health care that is much, much more inefficient than pharmaceuticals, and I can tell you why I think it's the case. When I go to Brussels, for example, to one of our industrial meetings and I mention the tellis train [sic], and I see that there is a new government somewhere and they need to find savings, I know they have a problem in two months because pharmaceuticals are the first thing that will come to us to bring the prices down. And there are many different tools that can happen. And I fully understand that that's the way it works, which is easy. So I think that's the way I'll respond to it at the end of the day.

MR. CORDERY: So long term, short term, medium term is how you have to look at it rather than just short-term savings all the time. Okay. We probably have time for one final question if anyone has anything to ask or any observations. If we're all done -- are you going for break or do you want to ask a question. Two quick questions.

AUDIENCE MEMBER: Mine is sort of off the wall. But I was sort of wondering, so we are talking about the U.S. subsidizing the rest of the world which is not exactly true but there's something there. One of the differences between the U.S. system and it has to do with payment is

we have a private system where the prices are mostly set through the private sector with insurance and most of the rest of the developed world and even emerging markets it's governments who do that.

Like is there thought within the U.S. of trying to push the rest of the world to move to a Medicare Part D system or something like that where actually you have private insurers doing the negotiation for prices? Because that's actually like -- like that would be more of an equalizing thing, or vice-versa, you could actually move the U.S. to the -- that would do a lot more work than a lot of other things we're talking about.

MR. PLICH: I will respond to that, not necessarily on behalf -- you know, I have quite a different part of the world, Europe. It's actually happening in many countries that operates in very similar ways. That's, you know, Netherlands is one of the examples, Germany is one of the examples, that you have the private insurers. Switzerland is another example that you have private insurers. And then there's government and then there's the medical so to speak in the age group that sets some rules. And then there is negotiations. It's just the role of the government may be much bigger as well, so there is -- still in Europe you have them do all the negotiations. In fact, you have triple negotiations because you negotiate with the government. Then you negotiate with the insurer. Then you negotiate with the pharmacy. And then you negotiate with even the hospital or God knows what more.

So that's the way it works. Now, coming back to your second part of the question, I think things may go on to the other way around. That the U.S. may inherit or may adopt some of the European ways of price medicines rather than the other way around.

MR. CORDERY: Okay. I think we're up to break time if that's all right. You can ask anything you like at break time but I think it's back here at 4 o'clock for the final session. So thank you all for your attention and break time.

[Applause.]

[Recess was taken.]

[Concluded at 2:46 p.m.]

PANEL VII:

SECURING INCENTIVES FOR NEW USES: PATENTS, EXCLUSIVITY AND/OR NEW APPROACHES?

Moderator:

Hon. Professor Sir Robin Jacob (ret.), *University College London (London, UK)*.

Panelists:

Professor Mondher Toumi, *Aix Marseille University (Marseille, France)*.

Dr. Galit Gonen, *Teva Pharmaceutical (London, UK)*.

David Rosenberg, *GlaxoSmithKline (Brentford, UK)*.

Professor Benjamin Roin, *Massachusetts Institute of Technology (Boston, MA, USA)*.

Bryan Zielinski, *Pfizer, Inc. (New York, NY, USA)*.

SIR JACOB: Well, this is the session where we sort of say, Well, what are we going to do about it? And the first thing that I'm going to remind you is what I said at the beginning, "it" was the creation of incentives for finding new uses for established medicines. We've heard of patent solution. We're going to hear about -- we've heard problems of the patent solution. I remind you

that probably the biggest problem of all is that you can't patent anything to do with an established use, you can't, in many, many cases because a patent has to be novel and not obvious, and often the starting point is in publication by a doctor saying, I haven't noticed this beneficial side effect so you can't get a patent.

Well, the team are going to come up with solutions. The intention is actually to take the solutions even further than just this, but let's go to the solutions first. And we have asked Ben Roin, who's thought about this and published about it longer than most people have, and so Ben is going to start.

PROFESSOR ROIN: So thank you for having me. Thank you, Robin. I'm really excited just, you know,

I've written about this. I've got a paper which I actually need to publish that's been sitting out in unpublished form for a while, and like any good law review article, it's a thousand pages long but it's 90 percent footnotes so it's not really so bad.

So this is going to be about solutions and, you know, I'm going to go in a particular direction which is not actually the specifics on whether we should use patents or regulatory exclusivity periods. I'm a big believer of regulatory exclusivity periods but not so much that, but it's going to be an underlying problem we need to solve in order to be able to deal with any of this stuff and we can do that, you know, we can see how to do that.

But before I do that, I actually just want to start quickly and remind us why we're here. And that's -- we've got a system designed to promote pharmaceutical innovation and it's really designed to promote the development of new drugs. Quite substantially that's what we did. We've got patents and we've got regulatory exclusivity periods and they're aimed at getting new drugs on the market. And the drawback to that is it turns out developing new drugs is like the single hardest thing to do in pharmaceutical innovation, maybe like in any form of innovation. Not only is it absurdly expensive and takes over a decade usually and has a failure rate that would make a Silicon Valley investor cry, but actually it's just like really hard to find novel compound structures that you can administer in the human body in a therapeutically efficacious dose without exceeding toxicity thresholds. That's just hard to do. It's the reason why medicinal chemistry has been the bottleneck in drug discovery for the past like 50 years, or one of the big bottlenecks in drug discovery, that's hard.

So we have a system designed to reward or encourage the thing that turns out to be one of the hardest things to do in this area, while at the same time we have tremendous progress going on both research in the clinician side and gaining a better understanding of drugs, both like their mechanisms of action and how diseases work and understanding different targets for treating diseases, understanding, you know, different sort of patient profiles and how you can sort of better personalize medicine. So we're gaining all this knowledge about that.

But we have this problem which is that, you know, we've got a finite patent term and so a quote from Janet Woodcock. "Once the generic competition occurs, any commercial incentive for further development disappears."

So as we gain better understandings of new disease targets and different similarities across different profiles and so, you know, we look at -- in the U.S. we have roughly 2,000 off-patent drugs at the moment and we can say, Gosh, I think a lot of these might actually work for some other disease and we're getting better at predicting that. Or we look at those 2,000 off-patent drugs and think, Gosh, I think some, maybe probably like most or all of those have personalized medicine applications. We need to do better in terms of knowing when to give patients those drugs and what

the dosage should be and who should be treated, you know, what mutations and the tumors or whatever that we should be looking at.

As we gain that knowledge, we don't have incentives to do anything with it if the drug is off-patent. And this is actually just sort of another quote which I think, you know, we haven't made the point, but it's worth making, so "If personalized medicine is only pursued by developing new drugs with companion diagnostics," so, you know, developing new drugs right now, "it will be a long time before this approach becomes the standard of care for most common medical conditions."

Like, if we have to develop -- instead of using the 2,000 drugs, off-patent drugs in our current arsenal, which in the U.S. represents about 80 percent of the prescriptions, instead of using that and trying to personalize that and finding new uses for that, we have to develop new drugs for all of this, that is a huge burden to put on our innovative community as opposed to, you know, just sing what we have with us.

All right. So what do we need? And I need to go fast, I know. So this is all --

SIR JACOB: You can run a bit longer. They're not that clever.

PROFESSOR ROIN: Oh, right.

[Laughter.]

PROFESSOR ROIN: I'm very excited to be here. I normally talk to academics and they don't know anything about this area and so I'm introducing all of it to them, and you guys actually do, so this is great.

So what do we need here? We want clinical trial data evaluating potential new uses in personalized medicine applications for old drugs, so we want those studies to be run. We want those things to be developed. We mostly rely on private for profit industry to make these types of investments. Of course, we could rely on the government to do it and the government actually does fund some of these studies, but honestly, the money just isn't there for the kind of investments we are looking for.

So we're going to talk about creating incentives for private industry to do it, not all of it but like a lot of it. The way we do this now is we incentivize private sector investments in new medical treatments by awarding temporary monopoly rights over those treatments. That's our system. We do that with patents and with regulatory exclusivity periods, that's the way it works. So what do we need here? We need either temporary monopoly rights over new uses or some other reward system that would serve the same function like prize system sort of with, I'm not a huge fan, but the paper is not about that and you can do something like that.

So I actually think it's worthwhile thinking about this in terms of two potential ways you could structure these monopoly rights. One of them is what I'm going to call standard monopoly protection for drugs. This is what we have. This is what we're used to. Standard monopoly protection is when you have a monopoly right that blocks generics from the market, so whoever the brand name company is, they have a monopoly on all sales for that drug because you can't get it from anyone else.

There's actually another type of monopoly right you could have which I would call indications to the monopoly protection, and we actually have these rights. They're awarded. But we'll talk about this. They're just hard to enforce and so we kind of ignore them. So an indication to a specific monopoly right would do one of two things. It would either give you temporary monopoly protection that block generic sales for a specific indication for the drug but not others. So the generics could -- you know, they could sell for a bunch of the older indications but you

couldn't use a generic for a new indication. Or you could actually and -- this would be same thing, it would -- just money would move around a little differently.

You can imagine a world where if a drug is prescribed for a new patented or protected indication, you could prescribe a generic for that, that's fine, but the payer needs to pay the branded company for that sale so you just move money that way. So that would be indication specific protection.

Now, this is just review. I'm going to go through this quickly. The standard monopoly protection that we warrant and use to encourage development of new drugs mostly is not available for new uses of old drugs, and this is all obvious to most of you, so you've got product patents on the active ingredient and formulation. If it's a new use for an old drug, obviously some of those are unavailable because the drug is no longer novel, the formulation is no longer novel.

Now, sometimes this works if the new use requires a new formulation, like you can't use the generic for the new use because it requires a radically higher or radically lower dose or a different route of administration, then it actually works and you've got a repurposing strategy and you can get protection over that. But if the generic works for the new use, you can't get patent protection over the product itself.

We've talked a bunch about this. You can get process patents over the new uses. This would be a patent covering -- well, in the U.S. you can and the protection you can get in other countries varies. But as we talked about, so this can work for the first use so -- but it doesn't work for subsequent uses because once the first use is generic, you can just use skinny labeling and get around it.

So basically all the generics you need to do is get approval for the drug for the old use, leave the new use off the label and they're not infringing the patent indirectly.

So the use -- we've actually talked about regulatory exclusivity periods. In other countries we haven't talked a lot about here, I need to go through this quickly. So the U.S. we've got four different types of regulatory exclusivity. You've got a three-year period for previously approved active ingredients. That's actually relevant for new uses. You have five years for new active ingredients, seven years for orphan indications, and that's actually going on to market exclusivity as opposed to data exclusivity which can matter.

The orphan exclusivity would also be available for new uses, so a new use that's an orphan indication, you would get that for seven years' protection and then 12 years for new biologics.

So much like new use patents, these are actually subject to the same skinny labeling limitation. All this protection does is says that the generics can't get approval for marketing for that indication, so if they don't ask for approval to market for the new indication, only for the old one, there's no problem, right. So that's the situation we're in with sort of the standard monopoly protection, it's just for the most part not available for new uses.

What I want to point out here is that there's actually good reason for that. That's not like an unintentional gap in the system. It's an intentional feature, and the reason why is that patents are supposed to link the private returns to innovation to the social returns. And the way this works is the patentees charge the customers, the people who are already using their invention, and so for all the people that are using it, they will pay based on the willingness to pay. So if you develop a drug and it's a breakthrough medical treatment for a very serious disease that's really common, you're going to make a ton of money. And if you develop a drug that's a minor improvement over existing treatments for a pretty uncommon disease, you're not going to make a lot of money because you'll have a smaller customer base and they won't be willing to pay. And that's the way the system is supposed to work.

When you reward firms -- so this would be an example where if you were to come up with a system where we're rewarding development of new uses for old drugs by sort of giving a monopoly right over all sales of that drug, by keeping generics off the market for longer, what you're doing is you're allowing them, the company with the longer monopoly rights, to charge not just for the new uses of the drug but also for all uses, and that actually breaks the link between the incentives for creating that new use and the social value you've created. And it does this other thing which is that we worry that you could actually have the perpetual monopoly protection.

The way you can think about this is, imagine if we have a system where you could sort of extend your monopoly period over a new drug, a drug you had already developed by three or four years if you develop a new use for it. What would have happened with Lipitor? Would Pfizer have ever let Lipitor go off patent? And the answer has got to be no. The board of directors would go nuts if the executives let that go off patent. You would constantly develop new uses for it. Some of it might be really important like maybe statins actually work for preventing cancer, that would be great, but some of it might be -- you know, maybe it reduces toenail fungus or something like that. If they could get three or four years for that they would, they would have to. And so that would happen and it would sort of never go off patent.

The other thing is some of those uses would allow them to extract huge amounts of money because they're not only charging for the toenail fungus, they're also charging for lowering cholesterol and diabetes and all that stuff.

So what does Europe do to avoid this? What Europe does is this they say, Well, we're going to have -- we're not just going to give you four years, we're only going to give you two and then one and you can only do it once or twice so we're going to limit the number of extensions you can do. That's kind of the solution they have in Europe where in America we don't do any of that. So imagine instead of it being Lipitor for toenail fungus, imagine what it is it's actually a pretty uncommon cancer drug for Alzheimer's. Are you really going to put a drug through Alzheimer's trials which are going to take five, six, seven, ten years, a long time, cost huge amounts of money, a lot of risk, for only one or two years of protection? Probably not.

So it makes it really hard to design a good incentive system in this set. So indication specific monopoly rights -- or monopoly protection is the right idea here but they're just hard to enforce, as we've talked about. So you can have indications of monopoly -- that preserves the link between the rewards for innovation and social value and you still have access to low cost generics in this space, for the old uses not the new ones. New use patents are actually sort of the easiest way to imagine this happening, where you could do regulatory exclusivity periods too. So the trick with these patents, and this is the way it works in the U.S., so they're directly infringed by the patients and sometimes the physicians but no one wants to sue them. Also you don't really know. They're indirectly infringed by the insurers and the pharmacists if they know about the new use patent and they know the physicians are prescribing the drug for the patent indication, which by the way you might think is a lot but actually increasingly that's the case with E-prescribing and prior authorization where those things are being disclosed.

The problem is that that infringement doesn't mean anything unless the drug company knows it's happening. The drug company needs to know that that sort of prescription there is infringement. If they can't detect the infringement, they can't enforce the right. So that's sort of the state of law in this place. And we have to build that and so what happens is we talk, Well, we could have these indication-specific monopoly rights but they're impossible to enforce so let's ignore it.

We definitely don't want to do that, and one thing I want to do is step back at this point and say, you know, once you see it like this you actually realize what's going on here. The problem

with new use is underneath all of this, use is subscribed once or a million times, right? You need to know that. And, you know, just build it into the patent system.

So if we can't observe the utilization rates, it's just very hard to come up with any kind of effective system in place, our patent system currently won't work, it would be hard to do a priority system rightfully. None of it really works.

If we solve this problem, our existing patent -- at least in the U.S., existing patent laws will kick in and provide actually a highly imperfect source of problems, with Robin pointed some out and there's quite a lot. But it was just something in this space, but you could also imagine us doing something different. Or you could also imagine us coming up with a better system. But we kind of need to get at these information problems first.

The other thing worth pointing out here is that once you realize that underneath this there's an information problem, you realize that it's much broader than just new uses for old drugs. Because it's not just old drugs that have multiple uses, it's new drugs that have multiple uses. Lots of drugs have multiple indications and those multiple indications are essentially different products. They're developed through different R&D investments. They require different clinical trials. They're delivered to a different set of patients and they deliver a different value.

And that last point actually is important because when they deliver a different value, they should probably have different prices. Value-based pricing sometimes also requires indication-specific pricing. We don't have indication-specific pricing, and the reason why is that the drug companies don't know when a drug is being prescribed for one indication as opposed to another. So if they were to negotiate with an insurer, Well, we'll bill a lot of money for this use but not so much for that other one, the insurance company would be like, Great, that's fine. What percentage of use were the low value uses? Well, all of them.

Like there's no way they could check so you're not going to get differential pricing because the drug companies just don't know, which is the same problem we have with new use patent enforcement.

And this is actually where it gets interesting. So once you realize that there's actually this kind of information problem underneath it, and it's a much broader problem than new use and it actually applies to patented drugs too, you say, Well, how does this play out in the market? In the U.S. at least, and I think this is also true but maybe operating in different ways in the EU and Europe -- or in the EU and in Japan, insurers, instead of negotiating lower prices for lower value indications, which they just can't do because the drug companies won't negotiate a lower price because they couldn't tell the difference between when it was expensive and not so it wouldn't work.

What they do is they impose access restrictions. They say, we will not cover the drug for this lower value indication, we're only going to cover it for these others, for the ones that are the most valuable or something like that. And that's actually -- in a sense that's bad for everyone. It's bad for the drug companies because they're losing a sale. It's bad for patients because they're not getting access -- if you want to use that for rheumatoid arthritis, you just can't. Insurance companies won't cover it even if it works for that. And actually it's not good for insurers either, at least if they can charge this, because they're reducing the value of their plan. They have less coverage. The more restrictions on access and insurers don't like that.

This is sort of going through. So what insurers do is they use something called prior authorization where they sort of demand access -- they demand doctors to tell them, you know, what is the indication behind this prescription, and if it's not covered, they won't grant access to it.

So as soon as we realize what's going on with prior authorization, also we realize that the underlying problem here, like we can't separate out the markets between an old use and a new use and multiple different uses. We realize that's a solvable problem and we know it's solvable because insurance companies here have already mostly solved it. Not entirely, but we can't really separate out the market between like a drug for mild back pain and moderate back pain, there's no way we can ever do that. But, you know, HIV and cancer, you know, brain cancer versus melanoma, Alzheimer's, like there's lots of markets we can separate and insurance companies are already doing it.

So how do they do it? Well, they only provide coverage for certain indications. They use prior authorization which they sort of say doctors have to report what the indication is. And they have access to the patient's health records. So if the doctor lies, they can tell, at least if it's visible on the health records, which it's like not always but a lot of times you can tell.

Interestingly, the PBMs say -- PBM, if you're not familiar, those are the -- in the U.S. they are the insurance companies for drugs. So we have Blue Cross Blue Shield or something else for most of your health stuff, but drug insurances run through these pharmacy benefit managers. They report that they have great success at preventing payments for drugs not provided for medically accepted indications by using prior authorization, when it's permitted.

So apparently it works, not always, but a lot, which means that third parties can in fact observe indications so we can have a system in place where we know the difference between Indication A and B and C and for that we have different prices, essentially by the way including when some of them are off patent.

I really need to go fast because I know I've gone over time and you guys are being super nice by not flashing the time.

So what would you do to do this? So one way would be indication reporting. This is not all that hard. Like E-prescribing enables -- so that's when you're just dispensing the prescription drug with no pharmacist through computer records. Those can have and frequently do have indication reporting features in them. And actually there is a study where they have mandatory indication reporting through E-prescribing in Quebec. And like apparently it worked really well so that's interesting.

E-prior authorization is another thing which is currently being developed and it looks like it's just through state laws and will be mandatory in a lot of these places. Again, it makes it really easy for not only management but for physicians to report indications when they're prescribing something. So, you know, once that information is down, that's really what we need so you sort of make that mandatory.

And I can think of two different ways of doing that: One, you could use the CMS regulations. Another one that I actually find a little bit more clever is you can actually imagine an FDA rule that says when a pharmacist dispenses a drug they need to have the appropriate labeling for the indication on the label that's given to the patient. And that would actually -- all of a sudden like if you had that rule in play, that would also enforce a whole bunch of things to happen. So Step 1.

Step 2 is the disclosure of that information to the PBM, because the PBMs already have this information, so it basically is giving pharmaceutical companies access to the reported indications and then also the -- and this is tricky, the health records. They would need to be able to see that. Because if you can't observe, if you don't have the health records, you don't necessarily know if they're lying or not. That raises privacy concerns obviously which I could talk about.

So the main thing you would do to deal with that is you would identify the records as available to the drug companies. So not so much with the health records but at least with indication reporting, this is less crazy than it sounds. With sort of the FDA -- the REMs rule, so when there's sort of a safety problem with a particular drug, it's actually not all that different from what we do now where the drug company needs to know to make sure that the patients who are being given the drug actually should fall within the category.

So we've had to do some stuff like this already. Like if you want to deal with privacy concerns, you can imagine expanding HIPAA or something like that. One thing worth noting here is this obviously doesn't work across the board. It does not work if you're trying to distinguish between moderate and mild back pain because like how on earth would you know whether a patient had one or the other? But it's definitely feasible in a bunch of places, including when the prescribing physician for one of the indications that you care about is a specialty doc, so that will right away tell you what the indication is.

Also particularly more serious conditions, you have concomitant or follow-up treatment that go along with it that will tell you right away like, this is prescribed for HIV, or, this is prescribed for cancer. You can tell the difference there.

And the other thing is that increasingly there's diagnostics being used along with prescribing and that's going to happen more and more. If there's a diagnostic in the health records, you can use that to tell. Right? So the idea is you could, from the health records, know what the indication is -- and insurers are already doing this, so this all seems feasible.

So then I'm going to end on this -- well, I have a thank you slide -- but before this, so what I've done here is I've said that if we can solve this underlying information problem that we should know when doctors are prescribing a drug for one of the patients as opposed to another, and that information can be made available to either the insurer or the payer, whether that's the state or private insurer and the drug company, you could separate out the market for these things. You could enforce new use patents. You could actually enforce regulatory exclusivity periods. You could do all that stuff. But without that knowledge it's very hard to do that.

But I haven't said the right way to do it. And there's a lot of questions here for how you would design this system. So one of them would be, you know, what should we use? Should we use patents? Should we use data exclusivity? Market exclusivity? Prizes? And I could talk a lot about this stuff because I read a lot about it. How long should the protection last? It's a little weird so we've got three years built in with data exclusivity in the U.S. for new uses. The patent term is 20 years. It's like there's a huge range and I don't know what the right answer is but this is weird just how big the range is.

What new uses should be eligible for protection? So this is actually what Robin was talking about a little bit earlier. You know, patents only protect new ideas. Regulatory exclusivity periods protect anything that wasn't previously approved by the regulatory agency. That's very different. So with patents there's going to be a lot of stuff that's normal and protectable. You also might have stuff that, like, shouldn't be protectable but technically qualifies as a new idea, whereas with regulatory exclusivity periods, that's actually like -- usually that's sort of what we care about because you argue you put it through the FDA, but you can imagine the use of that system in this context too. So it's an interesting question.

And then when should the protection be rewarded? Do we do it early with patents at time of discovery, or do we do it late with like FDA approval where either the regulatory exclusivity periods or it happens when you finish clinical trials?

Oh, and also, who should the rights be enforced against? So you can imagine, and this is actually -- so the second to last panel from before -- not the one before but the one before that, they were kind of talking about a system where you're enforcing patents over new uses against generics, which is an interesting way, but you can also imagine doing it against payers which is sort of more directly and I can talk that about that if people have questions.

Thank you.

MR. ZIELINSKI: Can you leave that last slide up?

PROFESSOR ROIN: Yes, sorry. Thank you.

[Applause.]

MR. ZIELINSKI: So what I'm going to do is I'm going to build on what he just said by giving a bit of the industry perspective so my main point is: Do we even really have a problem? There are many examples where second uses have been developed. A good example is finasteride, I think that was mentioned in one of the earlier presentations, one of the initial presentations. In that case, Merck, after they developed finasteride under the trademark Proscar for BPH, they discovered it could be used to treat hair loss so they filed a use patent. And they were able to do that and to stem cross label use.

Now, how were they able to do that? They came up with a different dosage so they went from five Megs to one Meg, and they also developed a new trademark, Propecia. But it's really the change in the dosage so that when the BPH indication went off patent, they had about some number of years left on the use patent for hair loss and it did not get significant cross label use so they were successful.

Another example is Viagra. Now, Viagra itself, as I think most people are well aware of, is itself a sort of second use. The drug originally went into clinical trials for cardiovascular indication and in the course of those trials it was discovered the patients weren't given the drug back and we had to ask them why. Oh, really? No, that's actually how it played out.

[Laughter.]

MR. ZIELINSKI: So we filed a use patent for ED and that became the primary use. Now, in the course of developing a drug for that, and really after it was approved, we also did a clinical trial for pulmonary arterial hypertension and the Phase 2 trial for that showed that the drug was efficacious for that, but the business did not want to develop it for that indication and the reason is because we couldn't get a patent. And so that indication, the pulmonary arterial hypertension indication would go generic in 2012 and that could undermine the ED indication which is -- which was projected to go off patent in 2018.

So that was a very significant worry, they wanted to kill that. But there was significant physician pressure to develop for that indication because it was so efficacious and so it became almost ethical to do it. And we did it and we developed a drug, but again, it was with a different dosage. So the dosage form, the oral tablet for pulmonary arterial hypertension was 20 Megs and the lowest dose for Viagra is 25. They're somewhat similar, but even when the hypertension indication went generic, we haven't seen significant cross label use that would undermine our sales for ED. So there was a success.

But these are exceptions. The norm is really Zoloft. Zoloft was an antidepressant. It was part of the SSRI class. Many drugs work by that mechanism but physicians actually have demonstrated that you get slightly different responses with the different drugs and we got a great number of indications for Zoloft. But we pursued virtually all of them during the exclusivity period for the product, and toward the end of the exclusivity period, we simply stopped. We might have

pursued a trial for Alzheimer's education but we just didn't do it because the worry was that we would never get a return for that investment. So that's a shame and that's the norm.

And in fact, we do have a case for OCD, obsessive compulsive disorder where eventually there was generic competition for the depression indication that was the first indication that's in the original patent. When that patent expired, the generic competitor introduced a drug with the skinny label directed to depression but they didn't include all the other indications including OCD. We see it on the OCD patent, obsessive compulsive disorder patent, we've demonstrated that the generic product was getting prescribed at the rate of 10 to 20 percent for that indication. We also even demonstrated the generic was aware of this and receiving a benefit of it, but it wasn't sufficient under inducement law at that time, and in present law too. And that's the way it is. You know, you're just not going to get a return for it.

So the solution ultimately doesn't really rest in the current patent law. It has to be -- maybe current patent law has a role in part of the solution but it's got to be something like this that's tied to how the drug is prescribed for the new use. That ultimately is the likely solution in my opinion. It can be a combination of regulatory exclusivity plus a prescribing change or it can be something tied to the patent too to determine the length of this period of exclusivity where you have the brand where it is somehow mandated that the brand drug be prescribed for the new use. But it's going to have to go beyond the patent law in my view.

And is that viable? Bob Stoll spoke earlier that legislation that is seen as benefitting the pharmaceutical industry is very hard to push forward, but I don't think it's impossible. He did mention that -- you know, he spoke briefly about patent reform and he said the pharmaceutical industry is pursuing this Hatch-Waxman -- pursuing an IPR carveout for all pharma products, biologics and small molecules, and he noted that it's just not going to happen. It's politically dead.

Well, he's probably right. But I think part of the reason for that is it's seen as just purely a benefit to the pharmaceutical industry. It doesn't tell a positive story. If you do have legislation like this where you can demonstrate that new uses, important new uses that wouldn't otherwise be developed would get developed, I think that you end up having a much better story even if the legislation scores.

And that's an important factor. For any new legislation in the United States, it goes through the Congressional Budget Office and they assess whether there will be a cost to the American consumers and that's called the scoring process, and legislation that scores is really essentially legislation that represents a cost. And often, if you introduce legislation to the scores; that is, it presents a cost for consumers, you have to have a pay for. And that's what they're looking for the IPR carveout, a pay for, some other legislation could compensate that.

I'm not sure that we would need a pay for this type of legislation, but one thing is clear, that we would have to tell a compelling story, and even then I don't think the legislation would move quickly but I do think there's a fighting chance and it's got to be something in the nature of this.

[Applause.]

SIR JACOB: Well, you got an insult to France earlier on. I'm not sure I go along with that but anyway you haven't got to answer the insult. Thank you very much.

MR. TOUMI: I do not have a chart to start nor a table of content. I commit not to oppose to any agreement and I will try to tell you a story.

Drug repositioning is something very common and it's not something new. If you look in the field of CNS, we identify in the recent research which is about to be published 109 CNS

repositioning drugs for 183 indications, and out of them 90 are under development. So this is something quite common. There is even some algorithm for classification about drug repurposing.

The other part is that health authority have endorsed and analyzed the value of second use. And in France, for example, you have drugs that have been -- that have received marketing authorization like for use in additional indication outside of the original indication of the product. Some of those products are off label and some are in label. So this is something well on the edge; however, there is a lot of resistance and this incentive to use these types of product or to develop these types of products.

We have two situations. Some of the product may be on patent and if you double up an extension of indication for such product, you will have to go through a new price assessment. It can trigger an SGS assessment, price reevaluation, and you will have fast erosion of your market share and manufacturer may not get return on investment. If you look at off-patent product, you have issues about the data protection and patentability which have been discussed, and even if you have a new indication, generic product may be used instead.

The substitution is in that case a critical issue and, again, manufacturer may not get return on investment. You have here a number of pricing regulation that may apply for this type of product and will all lead to price erosion in the different categories, I took the big five in Europe here, and if you come within your education for an old product, a natural product, a second use position, you trigger an HTA reassessment. You trigger price revision and usually because the price will increase you get the low price.

You will be requested to have a risk management plan. You will be requested in a number of cases to develop a pediatric plan. You may not get the new active status. And the price negotiation is often driven by the value of the historical product, even if thought it should be a value-based pricing process where the price would be driven by the value of the product.

Take here an example, Siklos. So they used to be a . . . company, an old product using oncology that has shown to be effective in sickle-cell syndromes and widely used in Europe for 15 years, but is totally not written for pediatric patients. The company has got an orphan designation and develop specific population for pediatric education and got an approval. However, in France the authorities compare the product to Israel and consider that they were negligible benefit over this product and end up pricing this product on the basis of the original old product. And the company got the price of 67 Euro for 1,000-milligram when the average paying price was about 10 years more. And this led to litigation procedure for about 10 years for the company to end up with 67 Euro at the end of the day.

So therefore companies are abandoning this field and going into the RER where there is no substitution to see to as much as possible that that product is not replaced by another product. So there is a lot of missed opportunities; however, we have a lot of value behind new use of mature product. These are cost effective products. They prevent the escalation of the therapy cost. They are to say faster, cheaper and less risky development. We get product with the safety that is well known. There is an important element as the decrease of labor use because often those products are used off label and this increased access.

I'll show you a few examples. If you get an old product and then a new one coming in or new invented product, you will have everybody switching from the other. If you have an interim step with products that are less expensive, you will have less patients switching to the third line therapy which is very expensive. So you have an opportunity to reduce the price of the product.

And one of the big issues is off label use. Off label use is -- is a good opportunity because you get an option to have a drug for a patient who had no treatment option. In -- relative in many

cases we have no evidence that it works, no evidence that it's safe. It's often inefficient use of resources. It creates opportunity, because some patients will have access to highly specialized center that will use off-label drugs while others will not have access to the center. And this is an issue that is currently growing. You have here a list of well-known products which are widely used off label. If you look here at the systemic product use for treating atopic dermatitis, the red ones are the ones that are used off label and you see there is much more red than black, and if you look at the U.S. guideline you see that the red one in the guidelines, recommended by the guideline, are all off-label product and this is not a very safe product. This product do carry some safety issues and should be very careful when using them.

If you look at the lupus, you can see here the same in red the product that are being used off label and in green the product being used in label. And if you look at the price of those products being used off label, perhaps limited, and you expect a new price of the new product and development to be more than 30,000 Euro per patient. So here off label use in chronic cough, everything in red is off label -- is off label, yes.

So we do have a possible solution. We have been able to create regulation for orphan designation. For product that develop new indication within the first eight years we have the opportunity for one-year market protection, but the pediatric development plan leads to additional protection. New active systems may be granted sometime without any grants and price differential has shown to be possible in a number of countries.

So here the example of Tecfidera, we do not have any ground to resell the new active substance status and because the Commission anticipated that the company may not launch the product if they don't get the status, they have granted the status on the basis of no grant. So things are possible.

You can see here the same product, Everolimus, with three brand names and different prices showing that difference in pricing is possible. It is possible even under the same brand. In Italy, for example, you can have specific agreement to obtain different price for the same brand. This is also possible in France and some other countries where the same brand has different prices through different regulation mechanism. This is something exceptional.

So incentives are needed. That would be different based if you have a product in the early stage of development, the first eight years. If it is in the following years after the first eight years or if it is a product where substitution is possible or a product where substitution is not possible, there is a clear gap here and we have to think from a public health perspective how to securely we can fill in that gap.

So second use of well-established product is real important for society and you have to think how we can capture this opportunity. It may be through different processes, from regulatory processes through incentive processes including for nonprofit organization. Thank you.

[Applause.]

MR. TELLEKSON: Good afternoon. I have absolutely nothing new to say but I'll say it for about five minutes.

SIR JACOB: It hasn't been said by you yet.

MR. TELLEKSON: Firstly, everything I'm going to say is because it's in my individual style, my personal views and may not be those of GSK. Secondly, unusually, I'm going to agree with both Pfizer and TEVA which will probably get me fired. It's the end of two days and it's been fascinating so let's have a little bit of audience participation. How many of you are not lawyers or IP lawyers or IP students? How many of you are not lawyers? Which shows why we have been talking only about patent law, essentially about patent law. And this morning we had really

fascinating stuff about patentability Swiss forms, construction, packaging, remedies for interim injunctions, filing injunctions and damages. Enforcement, Article 50, whatever it is of the EPC, fascinating stuff, but it doesn't really work, does it? It's all a bit blah blah blah when it comes to this issue. And it's a mess and it's a very expensive mess. For those of you who have followed the Warner-Lambert decision, a case that leads to 724 paragraphs -- 728 was it? I can't remember. That reached on just cannot be cheap to run. It serves nobody any use whatsoever except external lawyers, and I was one of them. And then I saw the dark side and went to the pharmaceutical sector.

What's worse than it being a mess, as Brian mentioned, the imperfections of patent law are actually driving research or driving research not to be done. That is not a sensible position irrespective of the ethics of it.

The second piece of audience participation, I'm going to put forward six or seven propositions and anybody who disagrees with them can put their hand up, okay? The first proposition involves a problem I think that we've seen. We've heard a lot of talk about patents and very little talk about the patient. This is all about improving patient health, Proposition No. 1. Anybody disagree? And the patents system should be about ultimately benefitting patients.

Second proposition: Repurposing or whatever we want to call it is important for patients and is going to become increasingly important over the next few years. Anybody disagree? That's great.

Thirdly, in the same system needed to develop new products and also incentives are needed to invent -- to -- incentives are needed to develop new uses for old products. Anybody disagree?

I would suggest and I'm not convinced to disagreement, that exclusivity is one of those incentives and pricing is another one of them. Neither is a solution to itself. Patents just aren't enough.

Fourthly, generics must be allowed to supply for the off-patent use. Anybody disagree? I might do just for the hell of it for some time. This is too easy.

Fifth, the innovator should supply for the on-patent use. Any of you disagree? And that's really where the tension comes in patent law, how do you balance those fourth and fifth propositions?

And the sixth proposition, and I don't begin to have an answer for this but it's the one Robin has raised every time. There are going to be lots of cases where we may be able to develop new uses but we will not get valid patents. I don't begin to have an answer for that issue, but does anybody disagree with that? Great.

So the solution, to use Jurgen's phrase was to -- I think you used "partition" or "segregate" the market. Can I suggest you don't use either of those when there's a competition order out? "Segmentation," I still suggest you don't use that word when there's a competition floating around, but that's what we have to try to achieve. And how do we do this? I don't think we're going to do it with patent law. I don't think we're going to do it by litigating against generics. For once, this is an area where I think the innovators and generics have absolutely common interests.

It really is one of those situations where we have a win-win-win. It's win for innovators, it's win for generics potentially, it's win for innovators. It's win for generics, win for payers, and most importantly, win for patients. But it's not going to be something for lawyers to achieve in court. It's far too important to leave it to lawyers.

It's not going to be about the technicalities of patent law because if you just look at Richard Arnold's judgment, which is beautiful in its writing and wrong. You can just see how difficult it

is. It was easy in Holland, with great respect, you can do a short judgment because you have 97 percent of the market but it's the wrong patent, but the 50/50 case is the difficult one. But it's not for Richard Arnold, it just failed for the innovator.

We've got to incentivize these new uses which benefit patients but I don't think we're going to do it by patent law alone. The answer is going to be even more difficult than patent law because it's going to involve politicians. Politicians are going to have to take action and it's probably going to involve something along the lines that Ben talked about, information available on prescribing and dispensing rules as to that. It's probably going to involve the sort of thing Adam talked about in premium pricing for the new indication. But because it's going to involve those two, it can't involve the European Union because this is not in the competence of the European Union. And I use the word "competence" in both sense, one, their power, and two, their ability.

It's going to require political will for legislators, either in legislation or in regulation, to spend public money for the benefit of the patients, and certainly in Europe getting public money spent when we're broke is very, very difficult.

I said at the outset Lord save us from the lawyers. I'll just finish by saying Lord save us from the politicians. And now the last piece of audience participation, polite applause, please.

[Applause.]

DR. GONEN: May I?

SIR JACOB: Yes. Big pharma and now we have generic.

DR. GONEN: Thank you very much. I'm not sure if I should be happy or not to be last.

SIR JACOB: We save the best for last.

DR. GONEN: First I would like to thank Jurgen again and I would like to thank Sir Robin Jacob for bringing me to them to co-organize with them this conference which was a great honor, extremely interesting and good fun. Jurgen grew a beard during the process. Sir Robin Jacob became a great athlete. You know, when I first met him I expected a helicopter and then we got a man on bike with a rain suit all wet, running and explaining that that's how he's saving time. He's doing his sport and bicycle and he's thinking at the same time, so it was good fun. Thank you very much.

So I thought long and hard what should I do in order to basically be last and still be interesting to you? And I attempted to do a recap of this conference and repurposing of drugs and try to centralize all the information in one place. How do I do this? Okay.

So introduction. When we talk about new users of established molecules, we're talking about incentives, and this was the talk in this conference so we talked about patents, regulatory exclusivities, prices; however, it is very important to remember the other side of the coin and the other side is access and access is as important as incentive and it is complementary to the incentive. And we are talking about access to pipeline, data and data mining, regulatory early access tools, funding, patent tools and potential timing considerations.

So I think Professor Toumi had by coincidence the exact same quotation that I have. I think we all support innovation for new uses of established molecules. The most fruitful basis for the discovery of a new drug is to start technology advances, the new transparency rules, early access programs.

Speaking on behalf of a generic company, TEVA, and this is in green not by coincidence, generic companies depend on innovation and generic companies fully support innovation. That's the pipeline at the end of the day that the generic companies are built on.

So incentives are required to support investment in finding new uses. The incentives should be in line with the size of innovation. I think also we all seem to agree on this. It should be balanced.

It should be balanced; on the one hand you want to incentivize, we really want these discoveries for society. Balance needs to exist with the benefit of generic entry to payers and to patients. And again, we have the other side of the access which needs to be -- needs to be kept in mind.

So repurposing is all over the media. We are not -- you know, we're not the only one who are talking the talk. It's in The Financial Times, The Guardian, Wall Street Journal, The Economist, all over the place. Everyone seems to be in agreement.

So going to the incentive sides, we're talking about patents, regulatory exclusivities and pricing, and here it is very important for me to say, and again, generic companies, TEVA, we do not oppose innovations. We do not oppose innovations on the specialty side of course but also on the generic side. We do not oppose incentives. Incentives are important. What we do oppose is unjustified abuse of the incentives to the TEVA competition, and this is something completely different. This is something which is very refined, but incentives overall are good for the industry and generic companies, and I'm wearing the generic hat for this statement, generic companies like incentives and agree with them.

So the first incentives: Patents. I think I agree with my panel friends here that we're not really discussing problem with the patent system as such. We are discussing issue with prescribing habits. We are discussing -- we are discussing problem with data. Data and prescribing habits. And the solution I think many of you mentioned, prescription by indication, and the thing is that in today's technology, this shouldn't be a problem. We have eHealth technology. We don't need to disclose to the other people in the pharmacy what was the indication. We don't need a conversation. It can be up an app with the iPhone, it can be somewhere in the software. Doctors should find it very easy to know what indication is patented or not.

And I think today we can actually make it happen, and there is an example for this. So the pilot is in Denmark. In Denmark that's the rules. We have substitution which is defined by patented indications. So when the indication is patented, basically the pharmacist who is the guard needs to dispense the brand drug. And it doesn't matter what the doctor wrote. If the doctor wrote the INN or the name of the brand, it doesn't matter. The pharmacist at his counter must dispense the brand drug. When the indication is not patented, then the pharmacy -- the pharmacist need to dispense according to the substitution rules in the country. So the cheapest, they want to tender, whatever the rules are, but there is a difference in prescribing and the problem was solved in Denmark, which is nice because it is a proof of concept so this works somewhere.

The second incentive is a regulatory exclusivity. The advantage in regulatory exclusivity is that can be in line with the scope of innovation. . And we heard within the U.S. it's five years for new molecule, three years for formulation. In Europe basically there has been almost nothing in terms of regulatory exclusivity. Jurgen challenged this, Stefano just yesterday. I think there is no reason why we shouldn't have it in Europe.

Again, when we talk about innovations maybe here an idea. As with orphan drugs we may need to show significant benefit or unmet need. So there seeds to be certification for the regulatory exclusivity. And just to say, regulatory exclusivity doesn't mean the information remains confidential, not at all. It just means that the generic company cannot use the results of the clinical trials in their filing and therefore their filing would be deficient by the end of exclusivity. Still, the clinical trials can be published or not, it doesn't relate at all to the existence of the exclusivity. Last incentive is the price, so even if we have a patent, and we have prescription by indication and we have regulatory exclusivity, at the end, if the payer is not convinced to pay the premium price for the indication then nothing is going to work. And I think this was the conclusion that if the industry agrees with the importance of the innovation for new users in established molecules, then this

should be the next talk. It should be a talk between the industry and the payers about paying premium for value. Adam mentioned that the current health technology assessments are only for new molecules, for example, in Germany. This is somebody that can be changed. Why won't we have health technology assessment for new indication? Why wouldn't we advocate for payment for value? So this is I think the next step on the way to having the incentive package complete.

Moving to access, which is again facilitator, the other side of the coin, and I think maybe it was a little less discussed in this conference and therefore I'm repeatedly emphasizing the importance. So we're talking first about access to pipeline. Here the example that I found, we're talking about collaboration between the industry academic institution with the government. The example that I found and wanted to present is the collaboration between AstraZeneca and the MRC in the UK, where AstraZeneca contributed research facility in Cambridge, they contributed pipeline, screening methods, and then the academy scientists have free access. There is an agreement about who will own the IP from certain innovation, Astra has first rights to market the product. It's an agreement which makes commercial sense. More companies then joined this corporation so Astra wasn't left alone. So this, for example, gives access to pipeline. This also promotes innovation. This is the other side of the incentives.

Second, for the access is data and data mining so we all -- we all are familiar in Europe, we have many initiatives of the European Medicines Agency in relation to transparency of clinical trials. Some clinical trials need to be disclosed with certain limitations. I actually want to be nice now to David Rosenberg, my panel friend, and say that we're not talking only about transparency rules by the EMA and data mining. There are other ways. For example, I think GSK was the first company that actually disclosed clinical trials as a reply to request for academic researchers. So I think the approach was that the company said, Researchers, you want to do research, come to me. You know, we will agree on terms. Whatever makes sense, at the end of the day you'll get what you need you, we'll do the research. So GSK was first to disclose its clinical trials in this scene which was privately agreed on but was very successful and then other companies followed.

Last, on data mining, I don't think we can have a slide on that data mining without mentioning the company 23andMe which is located in California. And this company specialized in genetic tests for private people and through this they collected an amazing bulk of data which, under confidentiality and agreement from patients, is raising now a lot of interest from the academy, from many institutions. Many are approaching them and want to use part of the data or some of it and now they started doing drug developments themselves.

And also TEVA, by the way, made recently a deal with IBM to set up a cloud for potential data collection on the basis of what's innovative technology and the thinking is that for a narrow degenerative disease, which is our franchise, we would collect data and, you know, who knows. This can lead to good things. So it's hard to define in advance but it's nice to have the platform to at least have the approach to collecting the data.

Then on access regulatory early access tools. So the European Medicines Agency in Europe is very much encouraging research in new uses and repurposing, and these access tools are actually the most appropriate for this kind of drugs because we're talking about safe drugs and therefore it's easier to accelerate the regulatory procedure. So we are talking here about some schemes which are creating a balance between timely patient access and sufficient data on benefits and risks.

I included all possible schemes here, present and future. I want to actually focus on this one. So this is a future one which is going to go to pilot next year and this initiative is basically all about talking at very early stage with our stakeholders. So instead of the company asking for scientific advice in a unilateral session, the AMA will talk with the developer about a development

plan, what exactly will be needed, which drugs can be done after the product is launched, payers would be part of the conversation, have technology assessment. It will be done right from the start so that the incentive would be kind of guaranteed from the start and the research will be very much encouraged.

For example, recently in Europe, there was a clinical trial in a drug which is called Lisinopril. It is used for MS and the clinical trials it was done as an open trial. Patients were at their homes reporting high end up and the result, so this kind of trials are more nuanced, more open, easy, less of an investment is required than the AMA is granted and there is a very diligent follow-up after the launch. But again for safe drugs, this may be the right access tool.

Just briefly to mention funding and the IMI initiative which is a corporation between the government and the industry in Europe, mostly a funding for malaria antibiotics, basically research areas which nobody wants to fund so they stepped into the niche and offered funding, which is also very important to -- for access.

And then patent pools. Also, this has a very specific context so this tool may fit for some situations and not fit for others. This specific patent pool is for HIV drug development for developing markets, and so basically the drug companies created a tool whereby they offered licenses for their patents to generic companies that can manufacture cheaply high quality medicines for developing countries and they get in return license fees.

So again, another platform to encourage development. It may not work in Western markets and the generic margin may not be so tempting to originate or grant license on but it worked for this purpose. It worked to advance HIV medicines for development markets -- developing markets.

And then here is my last slide, almost -- one before last where I try to preempt or pose questions so that I won't be surprised so I thought, what is left? So these are open questions. Timing consideration for third party developers. So say an originator drug invented a molecule, who should then invent a new use? Is it only the original company? Yesterday we heard about third party who developed a drug for Alzheimer's who was invented by another company. Should we encourage it? You know, I don't know that I have a view. I don't know that TEVA has a view, but I think that these are questions which need to be addressed.

What makes more sense? Our collaboration makes more sense when we talk about development of new users for established molecules because the research is slightly different than the basic research, and maybe we can grow markets and have win-win here, or maybe not. And again, some products can fit for some markets and some products and it may not be a right fit for others.

So just to conclude, we see that many, many initiatives, and in fact almost all initiatives in the health care sector today are relating in one way or another for research, for new uses in established molecules. So all the initiatives that I mentioned in Europe, tens of them are all concerning this subject matter, and if we succeed to solve it, then everyone is a winner. We're talking about the industry as a winner, the industry will have a more robust pipeline which is great for originator, great for generics. The patients of course, they will have more cure, proven benefits of drug. They will have timely access. Clinicians, they will not have to use off-label drugs, innovate, cutting pills, they will have safe drugs to use.

And then the health system, the payers, the general health systems, patients will stay healthier and will contribute better to society. So it's a win-win to everyone and I think let's get it done.

[Applause.]

SIR JACOB: Well, now, I did not know that Professor Toumi was going to produce a paper of that magnitude, that amount of research, that formidable heavyweight contribution for this debate. And I don't know, has it been published? Or is it -- was it still in the course of publication or what?

PROFESSOR TOUMI: I understand that it will be published. All that was presented here will be published.

SIR JACOB: But the basic work, is it in separate papers already?

PROFESSOR TOUMI: Many are already published.

SIR JACOB: I don't know that they have got sufficiently wide circulation.

PROFESSOR TAKENAKA: Is it in English?

PROFESSOR TOUMI: In English, yes, yes. Frenglish.

[Laughter.]

SIR JACOB: Frenglish, I've never heard of that. Frangli I can speak.

Because that is the case. We talked about in general that's the case. And I'll ask the panel generally, are we all agreed the patent system is not enough? Then the next question is, how are we going to do something about it? How are we going to get the politicians and the civil servants to realize this matters and that they can get more money, more value for their money by going down a route of providing the solution to this problem. Any ideas?

PROFESSOR ROIN: So I would say I think there's two things going on. So one of them is building an infrastructure where indications are imported, which you would want to sustain either using patents or regulatory specific periods or, you know, anything.

SIR JACOB: Yes. And we want that for another reason, don't we? Because if you record the indications, when you go data mining, you might find all sorts of things you didn't know.

PROFESSOR ROIN: Yes, it's good for health records, it's actually good for separate pricing for on-patent drug indications which actually turns out to be a thing that national health insurance companies and private health insurance companies really like because they -- and what they don't like is putting access restrictions on, they prefer to just have a lower price and they also think -- they actually think -- this may be right -- that they would save money if there was differential pricing by indication for off patent drugs, so I actually think that you have support for potentially.

Doctors seem to be the most resistant to that just because they don't like entering stuff that's tied to them, but I think they're going to lose that fight. And then so once you have a system, it's like, okay, we could separate the market for these things which is, Well, how do we want to do it? And I do think in the U.S. there's a slow moving but growing consensus that the patent system is not the optimal way of determining which drugs get protected and how much protection there should be.

I'm not a big supporter of that but it's been depressing to me how slow it's taking for that to sort of set in and the complexity of building a political consensus around that point, which it seems like everyone seem to agree with and most people seem to agree with, but like once you recognize that, you need to pick a number. So how much protection should things get, that is contentious, and it's very hard to separate out sort of the recognition that the way the patent system works in this space is deeply problematic and we can do better with regulatory specific periods, so let's pick a number.

SIR JACOB: How are we going to get the change then? How are we going to get the politicians -- we tried to get a congressman here but he didn't show. We tried to get the European commission. They cried off at the last minute. I don't know, maybe there was a good reason.

PROFESSOR ROIN: MODDERN Cures had just a 100 co-sponsors in the House, about 50 percent Democrat. It was like one or two more Republicans than Democrats. But there were 100 House members that signed up. So there's a push there. And when you think about it with MODDERN Cures, MODDERN Cures is a really interesting act. You know, 15 years is a long time.

SIR JACOB: Very long.

PROFESSOR ROIN: So you can imagine what if the number were 12, could you get it passed? Or, you know, 12 is the average amount of time a drug takes. So if the number -- if we pick 12 years until generics enter instead of 15, maybe that actually, you know -- and some people will say, well, it should be eight or seven or 10 or something like that, but 12 is sort of the average number. So maybe it's that -- maybe instead of getting 100 but it's not getting in the bill maybe you get 150 and it gets through. But again, what do I know?

SIR JACOB: Do you have any idea how to do something about it?

PROFESSOR TOUMI: I think the real problem is how to overcome the resistance and the resistance is that the pharmaceutical industry is having a very degraded image in the public, and there is a strong fear that this is a new trick to earn more money and cost more to the health services insurance and not necessarily deliver better health for the society and for the country. And you have to overcome that perception to make sure that you can start and have a constructive dialog. We say it's good to create health value. Who has an idea on how much value? Who measures it? Who attempted to measure it? Is it going to create savings? Who will try to measure that savings?

It's still a concept. And you have to move from concept to hard figures, and you have to, again, overcome the resistance, which may not be easy to make. And in my opinion it's more at that level that you can progress to get the finding regulation. Because solutions exist, many are possible. I've seen that in the past, but we need to create a momentum and a will and the right routes for the public that this is the right decision.

SIR JACOB: David, have you got any ideas about where we go next?

MR. TELLEKSON: It took us 40 years to do the UPC, it will probably take us the same to do -- no, I don't. In Europe I think there is -- and I'd love some of the European lawyers here to disagree with me but I think we have a real problem. There is no EU competence in this area, so it's going to have to be done in a member state, by a member state, particularly if we're talking about prescribing, dispensing or pricing. We can just about get a new incentive based on exclusivity through in competence terms, but that's not actually what we're asking for. At least I don't think what we're asking for.

So we're talking about 28 member states, or 27 when we leave next year, or when we vote to leave and then it will take five years to do that. But "I don't know" is the honest answer. Maybe the best way through is to start by saying we need incentives for certain diseases, just ask for limited scope of incentive, a limited remedy.

SIR JACOB: Pick some big ones which the public would vote for as it were, Alzheimer's or Parkinson's or something.

MR. TELLEKSON: You know me, Robin, I'm not entirely an optimist on anything, but I wouldn't be optimistic about getting anything done because, as you say, this industry has a dreadful image in Europe. Part of it's self-inflicted and part of it's not.

MR. ZIELINSKI: I think that -- I think one solution is do we actually have concrete data demonstrating the uses that -- something concrete to demonstrate uses that are not getting developed that would otherwise get developed if you had legislation like this.

Another thing is to make it reasonable in scope. You could pick particular therapeutic areas, that seems to be one mechanism that has had -- in the United States, and that also the period, Ben mentioned going to 12, maybe that would help. But then beyond that, I think it's advocacy beyond the pharma and biotech industry.

SIR JACOB: It is advocacy. The way you persuade people of things is never to talk about generalities, always tell them a story. And you're saying, well, pick some stories.

MR. ZIELINSKI: That's right.

SIR JACOB: Which is indeed of course where we began with Graham Russell who told us some stories.

MR. TELLEKSON: But I think one of the problems on that is if companies come out, and you've done it today and that's great, and I think Novartis has done it, when companies come out and say, we didn't develop a new indication because we wouldn't make money, we are portrayed as villains. And it's just the way the world works, that we will be castigated if we come out with a whole series of indications that we didn't develop.

SIR JACOB: And then you say, well, there must be a way of dealing with it. I mean Professor Toumi's thinking danger of off label use might be quite a good story for part of it.

PROFESSOR ROIN: Yeah, that actually is -- go ahead.

PROFESSOR TOUMI: I think it's a major public health issue and it's not really addressed. And in oncology about 30 percent of the drugs are used off label. And nobody knows what is the benefit and nobody knows what is the safety issues associated, but some guess, looks good. We know that a lot of product we guess they were good and never reach the market so you can imagine what does it mean? We guess it looks good without trials. Some have trials, but when we do the same trial in a double-blind randomized and respecting GCP, we don't find the same results. We know many of those stories.

So I think this is a real public health issue and I do trust that the main angle is public health. The lost opportunities of not treating, curing, improving patients with drugs that are available and the risk of misusing drugs to treat patients when we, in the best case, do nothing, and the worst case, we aggravate their situation.

SIR JACOB: Quite dramatic stuff, isn't it? Out there does anybody have any good ideas? Marino, you had an idea.

MR. MARINO: I should take my jacket off because I have to speak not as the EMA lawyer but as the former chair of the Trademark Committee at EFPIA. First of all, let me say I'm very pleased at the end of the conference, as I realize that for once generics and innovators sit at the same table and have about the same ideas. This was not the case in 2003/2004, when EFPIA was developing certain proposals for the Commission who was revising the legislation. And believe it or not, I was the one proposing to the Commission and the Parliament to introduce a mandatory brand prescribing where new uses of existing drugs were patented. And that was not only because at the time I believed in the inner value of pharmaceutical trademarks, but also because I knew that in the short/medium term not only Big Pharma but also generic manufacturers and in particular small/medium enterprises would have come and claimed for additional protection of these new uses.

At the time, after an initial moment of sympathy, the Commission was completely unable to listen to this proposal because the views of the EGA, European Generics Association and the views of EFPIA were dramatically divergent. It was impossible to say "a doctor must prescribe by brand if there is a genuine public health issue". What is the public health issue? The fact that, as you know, a drug must be prescribed and administered for the use for which it was authorized and

it was intended by the doctor. Therefore, if a company obtains a patent for a new use of an existing drug - with all of the difficulties that we heard this morning - , but then through off-label use the generic product is administered to the patient, I think we are basically betraying one of the pillars of the legislation of the directive.

The same unfortunate attempt was made again in 2011, when we were trying to convince the Commission that it was not good that in Article 14 of the "cross-border Directive" 2011/24 2011, 24, there was and there is a provision saying that the normal way of prescribing drugs should be by INN. Fortunately the Commission introduced a "public health exception", so if there are public health reasons then the prescriber should use the brand. And again, it was impossible at the time, only four years ago, to reach an agreement among the innovators and the generic manufacturers. Even the -pharmacists' association were shifting in favor of that but then all this collapsed.

As a result, several Member States introduced in their transposed rules, provisions saying that the general rule should be prescribing by INN.

So why am I making this long historical digression? Because I was fascinated to hear that, by Professor Roin I believe, that in the U.S. these ideas have already matured. I think there is a new political climate today. The Commission, a couple of years ago, enacted the "Better Regulation" path, basically one of the pillars of that document is that they ordered themselves to listen more to stakeholders and to enact legislation which is more consistent with the stakeholders' needs.

Now, if for once generic manufacturers and innovators are on the same line, we have a number of provisions that, if read together correctly, would be sufficient not to require a dramatic change in the legislation. If read together: 10.5 of the Directive (the one year of regulatory protection for new studies); Article 11(3) of the directive saying that the generic cannot have in the SMPC the patented indication; Art.6(1) and 87(1) of the Directive which say that a drug cannot be placed on the market and advertised for any other use than the ones authorized or intended, if you read together all these, all we need is to help the Commission and the Member States understand, as Professor Toumi was explaining, that this is a public health issue, and that the only thing that needs to be introduced is a mandatory system of branding, i.e. prescription branding where there is, I would say, not only a patent on the new or existing uses but when there is regulatory protection for the new uses. I have admired the efforts that have been made in Germany and in the Netherlands by the Courts even in terms of construing the EPC in a way that would be consistent with this additional protection. The judges should be praised for that, but I think the solution is not a patent-related one.

The solution must be administrative and regulatory-driven. Therefore, the effort should be to go for mandatory brand prescribing when circumstances are appropriate as we described. If doctors deviate from this mandatory rule, remember, the prescription is an administrative act, and if one makes a false statement on an administrative act, there are, according to the various jurisdictions, either civil or criminal or both, liabilities.

Insurers and payers would be happy because they would not be paying in vain, they would not be paying too much. And the patients should be happy because maybe they would have new drugs in the long term. Finally, in connection with electronic prescriptions, there is another instrument that 10 years ago was deemed unthinkable. This instrument is the currently called "Article 57 database", which the EMA is developing and it will be ready next year.

In the Article 57 database, which will be available to all Member States, all medicine or products registered in Europe will be recorded. It is a very user friendly instrument and will bear

all the strengths, all the dosages, all the route administrations, brand names, everything. So maybe 10 years ago this was deemed unthinkable. Now we have it and it may helpful in connection with electronic prescriptions to allow doctors to prescribe by brand name if appropriate.

Put all things together with the enormous power of the think-tank that Sir Robin is driving. I think the Commission will be happy to hear these proposals, but remember, if generics and innovators are not on the same side of the table, this will be again another lost attempt.

SIR JACOB: Thank you very much indeed. Not exactly a question but does anybody disagree with what he said? Because he's been saying the same thing that everybody has been saying up here. Well, audience?

AUDIENCE MEMBER: My idea for getting something like the MODDERN Medicines Act passed is to tie it to something that would rein in the companies that are engaging in what appears to be very opportunistic pricing, the companies that will purchase a product line and then increase the price by some very large percent, and I think that if the two were tied together, some measure to prevent that from happening, you would have a much better chance of getting something like the MODDERN initiative passed.

MR. ZIELINSKI: Can I address that one? You know what, this guy Turam [sic]? You know, he's not the pharmaceutical industry. He's just a rogue. You know, and so we would be completely supportive of something like that. The other thing that's worth noting, I think my colleague raised the question of what to do about uses that are experimental in nature that fall within say our patent, should that be allowed? You know, and the answer to that is we don't sue people for experimental uses and research uses. You know, within the pharmaceutical industry we're all working within each other's patents trying to do further innovation.

You know, that's not where the fight is. The fight is when someone's trying to come to market with an identical version of your product that's within the scope of your patents. It's not research uses. So I don't think that should be an obstacle either.

PROFESSOR ROIN: I would just say it was sort of strange to me, so when I came at this I would think of solving policy problems, like, okay, here's a problem and here's a solution to that problem. And one of the things I've learned is that, at least the way I think about it, it's not the way a lot of people think about it and it's clearly not the way they think about it in Congress. In there it's very much a give and take, so you're absolutely right. And we were talking about this a little earlier. So if you're going to do provision and it looks like this benefits one side, even if it clearly benefits everybody in some sense, like it's a good idea because you're solving a problem, if it benefits one side, then you actually kind of need to do something on the other side.

AUDIENCE MEMBER: That's my thinking.

PROFESSOR ROIN: Yeah, so that's what I was saying, so with differential pricing by indication, that actually -- on the payer side, they actually view that as good for them with unpatented stuff. So you have differential pricing by indication. So it's a cancer drug, it's expensive for this indication but cheaper for that one and cheaper for that one. Payers seem to really like that, but then once you get to so it's generic for certain indications and it's for others, so maybe that's the compromise there and, you know, then for picking for regulatory facility, yeah, we need to do something. Like there needs to be something on both sides of the equation.

AUDIENCE MEMBER: The other side of the coin hasn't been given I don't think sufficient prominence this afternoon and that is the cost of clinical development. There is an opportunity here to really go for the early access to medicine schemes. They're very well thought off; they are five schemes that Stefano said that are in operation now. If only the implementation of those schemes could be accelerated, the cost of clinical development would come vastly down.

There would be smaller studies, faster done, faster, more quickly performed and more maybe premature benefit risk assessments done. But that could be monitored because the operations are in place to monitor post marketing.

And that would itself improve trust in the industry if they don't constantly give these examples, which I think personally are exorbitant and inflated costs of development.

MR. FEHLNER: I was just thinking that there's another stakeholder here and that's the doctors. Now, you talk about some concern by the doctors are going to be regulated, they might be prosecuted if they don't fill things out properly, they get more paperwork, more burden. If that were not controlled, you might have a public backlash that for some reason the generics and the brands are getting together to somehow manipulate things. I'm wondering what outreach you would have to get the doctors on board on this?

DR. GONEN: Can I relate to this actually? So in my Danish example, the keeper is the pharmacist, not the doctor. So they made it with a smart software actually easy for the doctor so the patent indication, you know, is just a software and then whatever he prescribes, he prescribes, INN, brand. And then when it gets to the pharmacist, it is the pharmacist's duty for patented indication to dispense the brand product, whereas for nonpatented indication, the normal substitution rules are there. So it's not really a burden on the doctor who just uses a simple software, but the keeper is the pharmacist.

SIR JACOB: So I don't understand how that works. The doctor prescribes, and most times now a doctor just prescribes some medicine or other, five grams' pills, two in the morning, two in the evening or whatever it is, and the pharmacist just gets a box and puts the pills in and puts those instructions on it and he doesn't know what the doctor has prescribed it for. How does the pharmacist get to be the gatekeeper in this system?

DR. GONEN: It's electronic.

SIR JACOB: The doctor must say the five milligrams is for, whatever it is.

DR. GONEN: No, there is a patient file with what the doctor's write-up and then he just presses the right button and it's all marked. And by the way, when we talk about price, I actually forgot to mention it in my presentation, in Belgium there is a reimbursement by indication. So it's exactly the same thing when price is concerned. So the doctor has its conditional reimbursement and the doctor needs to, again, on software, quite easily accessible, needs to type indication and on the basis of which the reimbursement is decided.

So we have it already, it is just not all over the place.

MR. ZIELINSKI: Some prescriptions are still done the antiquated way where they fill out a little piece of paper and they just put in the therapeutic and amount. Sometimes prescriptions are written -- are done electronically. I was just prescribed Zithromax not that long ago and it was done electronically and the doctor just -- he didn't give me a slip, it was just already in. And maybe that's the best path forward to make it easy for doctors.

SIR JACOB: We have to make it very easy. I'm not sure threatening them with prison if they get it wrong would help, but I think most doctors would cooperate with this. And you're quite right, Garrett, that if this is going to be taken seriously you have to make sure there's not opposition from people that are going to get stuff on the red tops. And getting -- if generics and Big Pharma get together and say we have a common interest here and it's a public health interest, it's a patient interest and it's the doctor's interest because of that.

DR. GONEN: It's even more than this because it's the doctor's interest because the data is important -- regardless of the subject of the conference, the data itself, how many patients for each indication, the follow-up and the confidentiality concerns can -- again, is a big source today with

the methods of justification of date and utilization. We have tools for this which we didn't have 10 years ago.

PROFESSOR ROIN: Just add to this, this is actually I think an important issue and I had this paper and I actually got some hate mail from a couple doctors. The burden you're going to put on this, this is crazy, we're going to have to report indications, we need to be trained on this software, this takes so much time, it's going to ruin our lives. And, you know, a little reactionary. But like -- and one of the things I found actually, you know, people talk about the pharmaceutical industry's super powerful. If doctors don't want something to happen, they can stop it from happening. Doctors are super powerful in Congress because like every person, every politician goes to a doctor, goes to several. They have relationships.

So I actually think, and building off of our existing software and just saying, Look, if we're doing indication reporting anyway, and it is kind of happening, we're moving in this direction anyway. We have experiments with it, you know, the CMS is forcing U.S. doctors to start doing e-prescribing, they've got standards for that. e-prior authorization which requires indication reporting. A bunch of states have laws that are requiring supplementation. So you'd be working off of that and not doing something new. But there's something that actually -- and this is the most serious point of resistance I've found and I worry about, which is that, so imagine you've got a drug and it's a cheap generic for some indications and expensive for others. Doctors are kind of going to want to prescribe the cheap one, particularly if they think it's cheaper for the patient. If there's cost sharing in these insurance deals and it's more expensive so the patient has to pay \$90 if it's prescribed for one thing and it's \$5 for the other or free for the other, that is a really serious problem.

So I actually think one of the things that would need to happen in the space, if you've got expensive drugs for certain indications that are basically free for others, this is actually going to work, I think, but I'm not sure, but might require deals with the payers, with the insurers to not have expensive co-pays for the unpatented indications. Which they want to do because that's how they control utilization. They have to do other things.

But otherwise like it might not work or it would be hard. You need to actually have penalties. And, you know, some places those work and there actually are penalties now. So, you know, lying about the indication is fraud if it's Medicare/Medicaid covered and you can get in trouble for that, but more importantly, if it's privately covered and you lie about the indication, insurers actually bill the doctor for the cost of the drug if they catch them and then doctors complain about get audited. So stuff is already going on.

MR. TELLEKSON: I think that might be a very different situation in Europe. In the UK you pay a fixed price per prescription which I think is, you will be amazed, it's 12 pounds or something. I think -- but I think that varies from 28 member states. So the simple solutions we are proposing here may be simplistic simply because we have 28 different systems of prescribing, dispensing and reimbursing. So...

PROFESSOR ROIN: Yeah.

MR. TELLEKSON: But we get our drugs much cheaper than you do.

PROFESSOR ROIN: Not your generics.

MR. FEHLNER: You're welcome.

MR. TELLEKSON: There's incentives that make pricing reversed.

MR. FEHLNER: So we've agreed that patents aren't the solution here, but patents are a potential solution and I wonder how the panel thinks about doing what they do in other industries to facilitate access of competitors and that is something we don't often do and that's licensing.

Would there be an appetite to license our secondary patents, including the additional medical uses that we've developed, instead of trying to perpetuate continued exclusivity? And if we offered those licenses on fair and reasonable terms, would the generic industry take those licenses or would they resist?

PROFESSOR TOUMI: I think nobody would take it because it has no value because you cannot capture the value of it. That's the problem today, is you can't capture the value.

MR. FEHLNER: Why not? If they get a royalty on my license, why I'm not -- I'm not capturing the value I might have had, but as Pfizer has learned, they might not get that value anyway.

PROFESSOR TOUMI: You have an additional indication of a product that is already generic. How are you going to --

MR. FEHLNER: So I'm only talking about in this question, licenses to the patents I have, the portfolio of patents I have on my product for the approved purposes, which I may have gotten approval for more than one indication. Oftentimes companies do multiple indications, either multiple kinds of cancer or we talked about overall and I saw the slide up there. There's three really very different indications for that drug. What if I offered licenses instead of litigation?

SIR JACOB: Licenses for what? For new use or the existing use?

MR. FEHLNER: The existing uses, but to facilitate the generic entry. And I still get some reward from that. Instead of spending millions of dollars on litigation, I'll get a small amount of money in royalties. It's not going to be the same amount of money I would get for exclusivity, but it would be something. And we talk about the generic -- sorry -- the innovator industry having a black mark. Would this help the innovative industry perhaps better its image by not fighting for the last -- to the last breath for exclusivity?

DR. GONEN: I would think another motive of, if we are talking licensing, I just think that a simple license would be problematic because the generic margin is tiny and I don't think it would be sufficient to make it worthwhile basically, at least in Europe. But I can think of a different model whereas the originator has his patent to the original drug and then it licensed the patent to a generic with capability of research for new uses, and then the generic incurs the investment of the new use and they split the profits on the sales.

And it doesn't monopolize the market for the old use, we just talk about different patient population so basically the generic made investment, the generic grows the market. Everyone wins because the generic would have basically derogation for the sake of manufacture from the original exclusivity and then really the license fees can be beneficial because they would come on top of the original branded market. So I think this is a deal model which can be thought of at least --

SIR JACOB: But it all presupposes that the thing is patentable, the new use. I mean the real problem is if that won't work, if it's not patentable because the generic spends the money getting the benefit of new use and another generic comes in and says, well, thank you very much.

MR. FEHLNER: Right, and it does presuppose there's a patent to license, absolutely.

MR. ZIELINSKI: If you did get the patent -- so to some extent this is already happening already. Most of our litigation we ultimately sell, at least with respect to the secondary patents. And with respect to the new use, quite often we have limited development dollars. People -- it's already been pointed out that development is the most expensive part of the R&D equation by far. It's like 80 percent of the cost of R&D is in D, is in development, which you know. So we're always looking for ways and other pharmaceutical companies are looking for ways to defray the cost of development. In part, one way to do that is risk sharing through that type of arrangement and we

do that. And so it would be a natural extension to what's already happening to do just that. So I'm assuming we would go down that path.

MR. FEHLNER: Then I have just another thought and that is listening to Gates yesterday, is that a potential model for these additional uses that are dormant years after all patents have expired around a product, potentially a generic public partnership where there's public investment either from payers or governments or both with a generic company that's capable of doing some development work? And we're talking about definitely less expensive development, right? We already know the safety profile of the drug in principle, it's just to get on-label additional indication.

And then kind of what would the potential rewards be? Differential pricing is an interesting one but that's a pain in the ass, and we know that if there's differential pricing we're going to get arbitrated. How about just exclusive sales into that indication? If you're managed it through the payers and managed it through the governments, whoever is paying for it, you can have that kind of exclusivity. And Brazil does it already through their tech transfer model. In return for transferring the technology to manufacture a drug, Brazil guarantees you five years' exclusivity to supply that drug to their health care system. So the model could potentially work and it does provide a mechanism for getting these additional uses without having to worry about differential pricing but the generic company expands its market and has exclusivity in that expanded market for some period of time. I would be interested in your thoughts about that possibility. Thank you.

PROFESSOR TOUMI: I think there's an interesting example, the example of Lucentis and Avastin that everybody knows. Avastin was a drug by Roche and Lucentis, which is an Avastin B, was licensed to Novartis. So if you look at what is happening now, you see in UK they have studied to study to compare Lucentis and Avastin. In France, the minister of health has granted marketing authorization of Avastin for ophthalmology; despite they don't own the product, they provide the right for the physician to use it in this indication.

So I'm not sure it's the solution. If you look in Norway, the authorities are making the study to look at the substitution of GNF to show that when you substitute bio similar there are rules. If there is a risk, at least measure the risk and they anticipate low risk. In France, the government has suspended a study to assess the value of baclofen for alcohol withdrawal syndrome. I think there is a risk that tomorrow such indication will be funded by health authorities or by nonprofit organization and become available for free to everybody. There is not clear action and attitude from the pharma industry to show that there is a real public health issue and there is a real benefit for the society, and this is not a trick to prolong the patent life or the exclusivity life of such product, so there is no action to rest in that direction. I'm sure that it will happen. And I see already clear trends of when the government of funding, supporting the development of such product to create evidence that they work and provide the necessary information to allow physician to use them off label but with robustity. If nothing is done on the industry side, this would be the direction you would go.

SIR JACOB: Well, now, I'm supposed to do a wind-up unless anybody's got some burning questions. I think everybody is completely worn out. Two days -- that's a cell phone. When I used to sit in court you would threaten people with that.

MR. TELLEKSON: Why should you change now?

PROFESSOR ROIN: That's when you had power.

SIR JACOB: Two days of very intense -- and very constructive towards the end, I thought, of exposing the problem, exposing -- I felt this morning a bit discussions of angels as the lawyers talked. Swiss form claims which are obviously a branch of metaphysics really. Do you know what

metaphysics is? It's the physics that nobody do so you just call it, you just debate it all the same, things you can't measure. But towards the end of this second day, we've had extraordinary measure of agreement in a way forward. It's not for me to do that, it's not for most of us, but it is possibly for generics and Big Pharma to get together I think probably with Garrett's suggestion of maybe getting the doctors on site before they start howling, and then maybe at the end of it all we might solve the problems which Graham Russell began with, but not only for the bisphosphonates, but for all other medicines.

Again, this could not have happened without the sponsors, without the ideas of the sponsors, and it couldn't have been any good without the audience and it couldn't have been any good without Washington University, and it couldn't have been any good without the people from Washington University. But it has been quite extraordinary and I think there may be another such conference but I hope if and when it comes, we're further down the road. And that depends upon generics and Big Pharma getting together. Of course all competition will lie and say, You're crooks in the first water but making the case for getting more value for the public money that is being spent on -- or the private money that's being spent on medical care and the better medical care, and if we can do that we've done something.

Thank you all very much indeed for coming and thank you all for being such fun too.

PROFESSOR TAKENAKA: Thank you very much.

[Applause.]

PROFESSOR TAKENAKA: Again, it was a big honor for the University of Washington to host such a wonderful conference, very interesting conference on such an important topic. Before closing, I would like to acknowledge special people, associate director of health law program Mr. Terry Price.

[Applause.]

PROFESSOR TAKENAKA: As well as, I don't know if she's still here, but I would like to thank the director of CLE program and the conference, Ms. Kathy Kline, students from the LTA journal, in particular Ms. Kris Lee who helped preparing the conference. I hope that, you know, this discussion will continue somewhere in the United States or Europe or Asia. Thank you very much again.

[Applause.]

[Concluded at 4:56 p.m.]

